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# EFFECT OF VARIOUS SULFONAMIDE COMPOUNDS ON NERVE REGENERATION

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This study was undertaken to determine whether the use of sulfanilamide, sulfathiazole, sulfapyridine or sulfadiazine has any effect on an injured peripheral nerve and its adnexa. It has become a frequent practice to use one or more of these drugs locally in routine operative procedures and in treatment of war injuries. Although their use in wounds of these types has been considered as harmless in general, despite the occurrence of a serous exudate (Key and Frankel [1]), the specific effect on nerve regeneration has not previously been evaluated.

## MATERIAL AND METHODS

The sciatic nerve of the cat was selected for the present experiments. One sciatic nerve of each animal was treated with 0.25 or 0.5 Gm. of one of the powdered sulfonamide compounds previously mentioned. The other nerve was left as a control. All operations were carried on under aseptic conditions.

Appropriate experiments were designed to determine the local effects of the drugs following simple nerve section, primary suture and suture delayed five days after the injury. The 58 animals used were killed at intervals of two, five, ten, fifteen and thirty days after the operation. Alternate longitudinal sections and cross sections of the nerve were stained by a modification of the Bodian silver method for nerve fibers (Ungewitter[2]), the hematoxylin and eosin method, Masson's trichrome technic and a silver impregnation method for argyrophilic and collagenous connective tissue.

## OBSERVATIONS

*Nonsutured and Sutured Nerves.*—Two Days After Operation: Some nerve fibers showed an early stage of regeneration, with typical growth cones at the tip of the axon. These regenerating fibers had not grown any appreciable distance and did not enter the distal stump of the nerve even when the latter had been sutured. Some retrograde degeneration was going on in the central stump of the nerve, but this appeared to be negligible in amount and did not extend far centrally. Distally, the axons showed fragmentation and typical degenerative phenomena, but the degenerated portions had not been removed by the phagocytes. Many fine fibers in the distal stump did not show any signs of degeneration; presumably,

From the Department of Anatomy, Cornell University Medical College.

This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Cornell University Medical College.

1. Key, J. A., and Frankel, C. J.: The Local Use of Sulfanilamide, Sulfapyridine and Sulfamethylthiazole, Ann. Surg. **113**:284-297, 1941.

2. Ungewitter, L. H.: A Controllable Silver Stain for Nerve Fibers and Nerve Endings, Stain Technol., October 1943.

these were the autonomic components of the sciatic nerve. A few intratubular phagocytes were present.

The tissue surrounding the nerve showed a typical acute inflammatory reaction, with a large number of polymorphonuclear leukocytes and a smaller number of other leukocytic forms. In the sutured specimens, the inflammatory reaction seemed to be limited to the peripheral structures of the nerve trunk; there was no notable invasion of the nerve trunk itself. In nerves which had been treated with a sulfonamide compound there was evidence of degeneration of the leukocytic forms which were in the immediate neighborhood of the drug. Pyknosis and nuclear fragmentation were the outstanding characteristics of this degeneration.

There was already beginning organization of the blood clots in nerves which had been treated with sulfanilamide. Blood clots in nerves treated with other sulfonamide compounds were not yet organizing. Sulfanilamide had been absorbed, but the other drugs had not.

Five Days After Operation: All the nerve fibers showed signs of regeneration, except for the few which were still undergoing retrograde degeneration. There was an apparent multiplication of fibers, due to numerous fine and small fibers which stemmed from the thicker ones. In well sutured nerves the regenerating fibers had already penetrated the distal stump. In nonsutured nerves the failure to penetrate was expressed by a spiraling of the fibers within a neurilemma sheath. This spiraling is characteristic of the so-called structures of Perroncito. Also, the distance between the cut ends in nonsutured nerves was greater than the distance which the newly growing fibers had been able to traverse. Some of the original fine fibers were still present in the peripheral stump, but not many.

The acute inflammatory reaction was subsiding. The presence of many mononuclear forms suggested low grade chronic inflammation. The nerve trunk was not invaded by these inflammatory cells. There did not appear to be any particular migration or change in form of the Schwann cells, either in the central or in the peripheral segment of the cut nerve.

Some fibrosis had appeared in the region of the injury. Most of the connective tissue in this process seemed to stem from the epineurium. The perineurium may have contributed slightly, but the endoneurium did not appear to be involved at all.

Intratubular phagocytes were more in evidence, especially in the distal stump. These phagocytes filled up the old myelin sheath and thus may have barred the passage of regenerating fibers. Karyorrhexis was still evident in those specimens in which the drug had not yet been absorbed. This was purely local, not extending beyond the immediate neighborhood of the drug and affecting only the leukocytic forms which were apparently trying to remove it.

Ten Days After Operation: All the nerve fibers, both on the treated and on the untreated side of all the animals, appeared to be actively regenerating. The progress of the fibers into the distal stump of a sutured nerve was more rapid than the removal of the debris present in that segment (fig. 1 *A* and *B*). Many of the old sheath canals were still filled with intratubular phagocytes and fragmented portions of the axons. The new fibers appeared to pass down alongside of, but not within, the old sheaths. These fibers, however, were related to cells, presumably sheath cells. In some cases this relation was so intimate as to suggest that the new fibers were actually intracellular.

Fibrosis was more marked at this time, being still more closely associated with the epineurium than with the other connective tissue sheaths of the nerve trunk. This fibrotic growth was more conspicuous in the nonsutured nerves and presented a barrier to the penetration of the nerve fibers into the distal stump.

Some giant cells had appeared in the treated nerves of these animals. The cell types present were indicative of chronic inflammation, probably a foreign body reaction. Karyorrhexis was still present among the leukocytes adjacent to the unabsorbed drug.

Fifteen Days After Operation: Considerable numbers of nerve fibers had penetrated the distal stump of the nerve and had progressed a great distance along it in the sutured specimens. It was rare, however, to find a new fiber in an old neurilemma sheath. Some new sheaths seemed to be forming from old cells, but the majority of the fibers did not yet have a specific sheath, although they were in relation to sheath cells. There was little penetration in the nonsutured specimens. Distally, the debris had been fairly well cleaned up, and many intratubular phagocytes were present.

The connective tissue was heavy and dense—located peripherally in the sutured nerves but lying over the cut ends in the nonsutured ones. Irregular

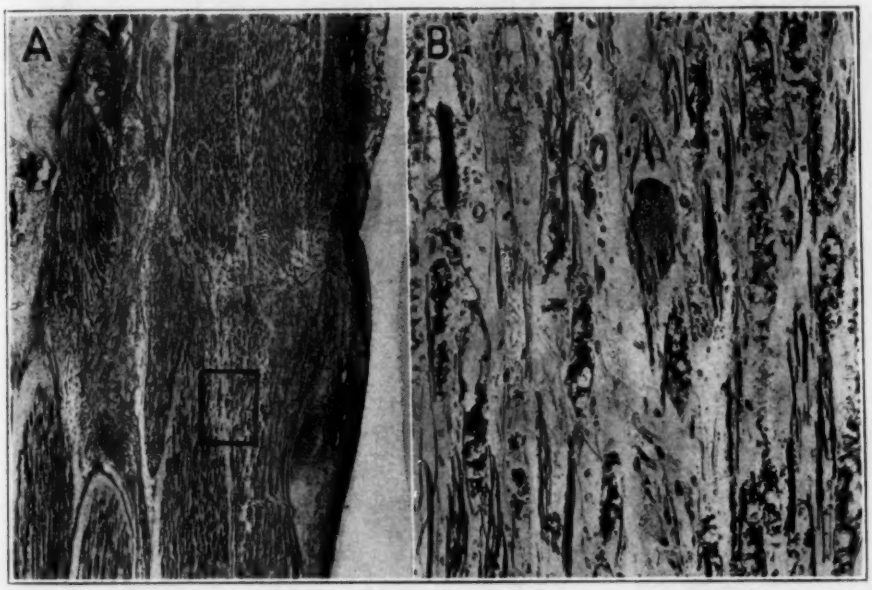


Fig. 1.—*A*, suture line in the sciatic nerve of an animal killed ten days after section and suture of the nerve. The central end is at the top of the photograph. The rectangular area marked is shown in *B*. Silver technic; × 16.

*B*, area from *A*, showing many new nerve fibers entering the peripheral stump and passing down alongside the old sheath tubes. The latter are still filled with debris of degenerated axons and myelin. × 175.

formation of connective tissue offered considerable hindrance to the passage of nerve fibers, and the number of the structures of Perroncito was good evidence of this connective tissue barrier. Such spiral structures were common in the nonsutured nerves (fig. 2) but relatively infrequent in the sutured ones. Some connective tissue bundles were arranged roughly parallel to the axis of the nerve, possibly as a result of tension or stretching, and some nerve fibers could be seen following the bundles thus oriented. The regenerating fibers had become lost among the bundles which were more irregularly placed.

Thirty Days After Operation: There were good regeneration and penetration of the distal stump in the sutured nerves. Some fibers had managed to bridge the gap in nonsutured nerves, but in much smaller numbers. Even in some of the

sutured nerves fibers had failed to penetrate in some bundles, owing to displacement of their cut ends, in which case the bundle consisted almost exclusively of "sterile" tubes (fig. 3 *A*), whereas in cases of good contact there were numerous

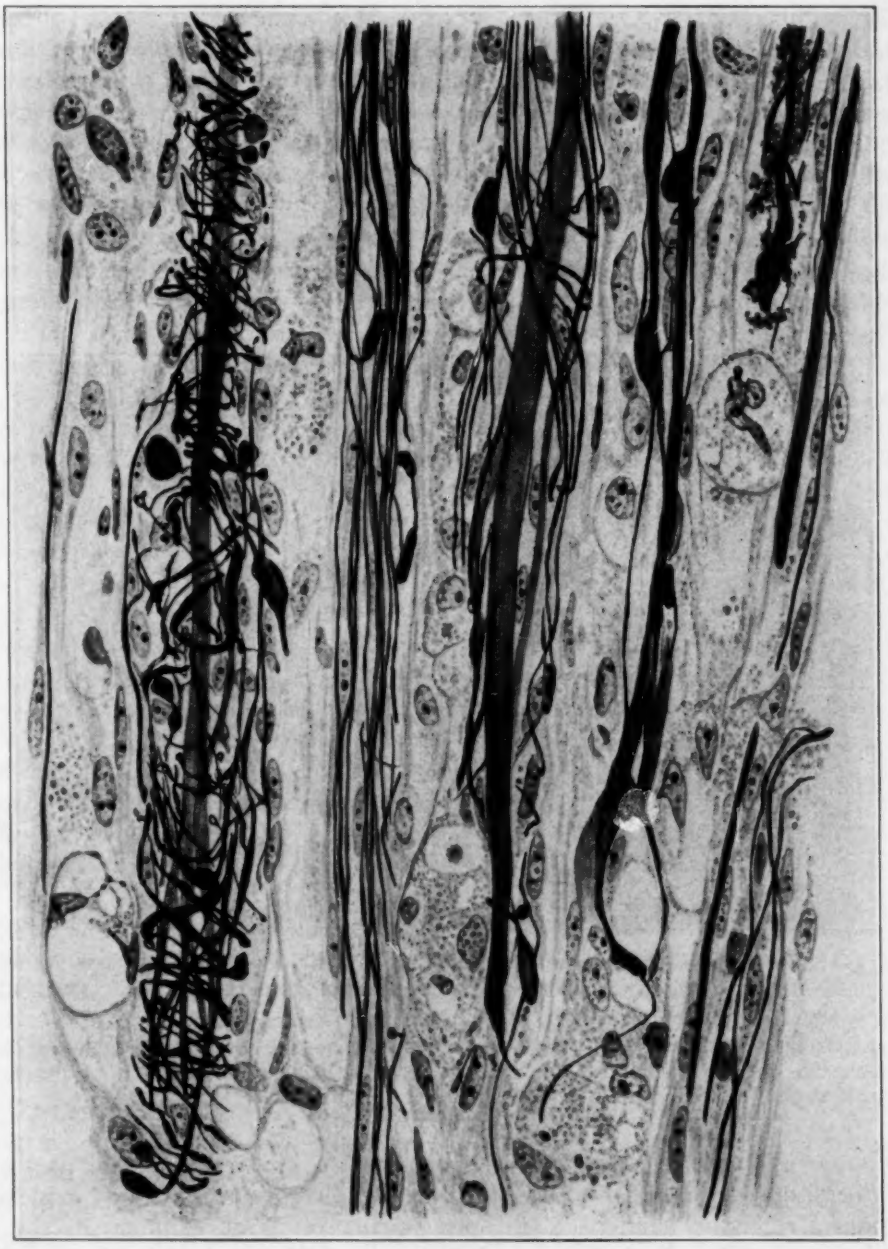

Fig. 2.—Drawing made ten days after operation, showing structures of Perroncito in the central stump of a nonsutured nerve which was treated with sulfapyridine. Silver technic; × 445.

nerve fibers (*B*). The caliber of such fibers was still small. There were a few medium-sized fibers, which seemed to have a thin myelin sheath and a neurilemma. Occasionally, several small fibers lay within a common neurilemma sheath. Most

of these sheaths seemed to be newly formed. There were many old and unoccupied sheaths containing phagocytes (fig. 3 *C*). In other areas the nerve fibers apparently coursed within the schwannian syncytium previously occupied by the nonmyelinated

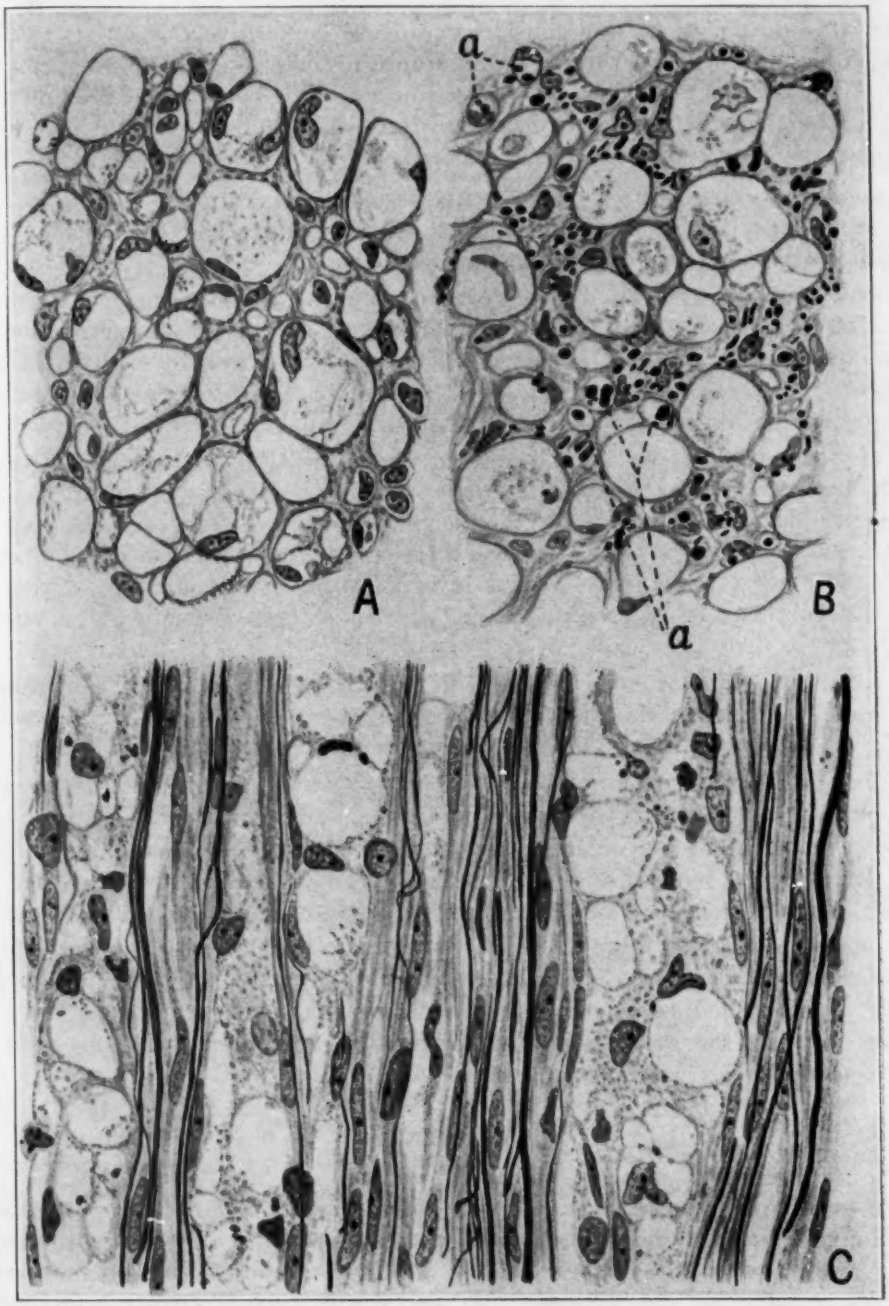


Fig. 3.—High power drawings of fibers in the peripheral stump thirty-one days after operation. *A*, "sterile" tubes in cross section, from a bundle which was accidentally displaced at the time of suture. Regenerating fibers occur in the epineurium but have failed to penetrate the nerve proper. *B* (from same section as *A*), position of regenerating axons in another bundle in which the penetration was good; *a* indicates medium-sized tubes, containing regenerated axons. *C*, longitudinal section of a peripheral stump of the nerve treated with sulfanilamide, showing regenerating axons between tubes filled with phagocytes and debris. Silver technic; × 445.

fibers of the nerve, singly or in groups. A narrow, empty space around each axon possibly represented a young myelin sheath, but it may also have been due to shrinkage of the axon and the schwannian syncytium during the preparation of the specimen.

In all animals, there was considerable dense connective tissue. Its peripheral location in sutured nerves offered no hindrance to the passage of regenerating nerve fibers. In nonsutured nerves (or sutured nerves with poor approximation), there was only slight penetration of fibers into the distal stump, owing to the presence of irregular, dense connective tissue between the two segments of the nerve.

*Delayed Sutures.*—Five Days After Second Operation: These specimens may be compared with those in which a primary suture had been made and the animals were killed ten days after the operation.

Considerable regeneration was going on, almost all fibers being affected. In the untreated nerve some fibers had penetrated the distal stump but had not grown quite as far as those in nerves with primary suture. In the treated nerve, however, the fibers had been unable to penetrate the distal segment, owing to the interposition of some of the unabsorbed drug.

There appeared to be a low grade traumatic inflammatory reaction, probably due to the second operation. This reaction corresponded to that seen in animals killed five days after section of the nerve. Otherwise, save for the extent of penetration of the nerve fibers distally, there was no significant difference between these nerves and the nerves with a primary suture from animals of the same age. Karyorrhexis was present, as usual, in the cells around the unabsorbed portion of the drug.

Ten Days After Second Operation: The regenerating nerve fibers had not been able to penetrate the distal stump quite as far as those in nerves with an immediate primary suture. The histologic picture was otherwise identical.

Twenty-Five Days After Second Operation: Although there was a rather dense formation of connective tissue, it had apparently offered little hindrance to the penetration of the regenerating nerve fibers (fig. 4 *A* and *B*). This connective tissue was more often regular than irregular. Stretching may have been responsible for orientation of the connective tissue bundles in this fashion. The nerve fibers seemed to follow the path of least resistance, which was along the direction of the collagenous bundles parallel with the axis of the nerve. The inflammatory reaction had completely subsided, although some giant cells were still present. Except for the distance of penetration, this series of nerves differed little from the series with primary suture.

## COMMENT

The regeneration of nerve fibers in the cat did not vary from the usual pattern even in the presence of the sulfonamide compounds which were used in this study. In fact, no difference from the normal could be detected in the treated nerves after a careful histologic study. From the central end of the severed nerve each axon put out multiple fine fibers with typical growth cones, which grew down toward the distal stump. These new fibers traversed the forming cicatrix between the cut ends to reach the distal stump by the end of the fifth day if a suture had been made. (If the cut ends had not been approximated by suture, it might be thirty or more days before new fibers could bridge the gap between the central and the distal stump.) This growth and progress of the

regenerating fiber agreed with the observations of Huber,[3] Ramón y Cajal,[4] Nageotte[5] and others, who have worked on regeneration of nerve fiber. Huber made an excellent study of regeneration of nerve fibers within various grafts.

Although no chemical effect on the nerve fibers could be observed, a mechanical influence was probably introduced by use of the drug in a wound of this type. This mechanical effect was dependent on the rate of absorption of the drug. Sulfanilamide in the dose used was absorbed within forty-eight hours and did not influence the type or the rate of regeneration in any way. The other sulfonamide compounds employed, however, were absorbed much more slowly. These drugs, when present between the cut ends, retarded or prevented the passage of new nerve fibers in the same manner as a dense connective tissue mass might prevent it. The tissue around the drug responded to its presence as it would to any foreign body, with fibrosis and production of giant cells. This response was somewhat tardy in its

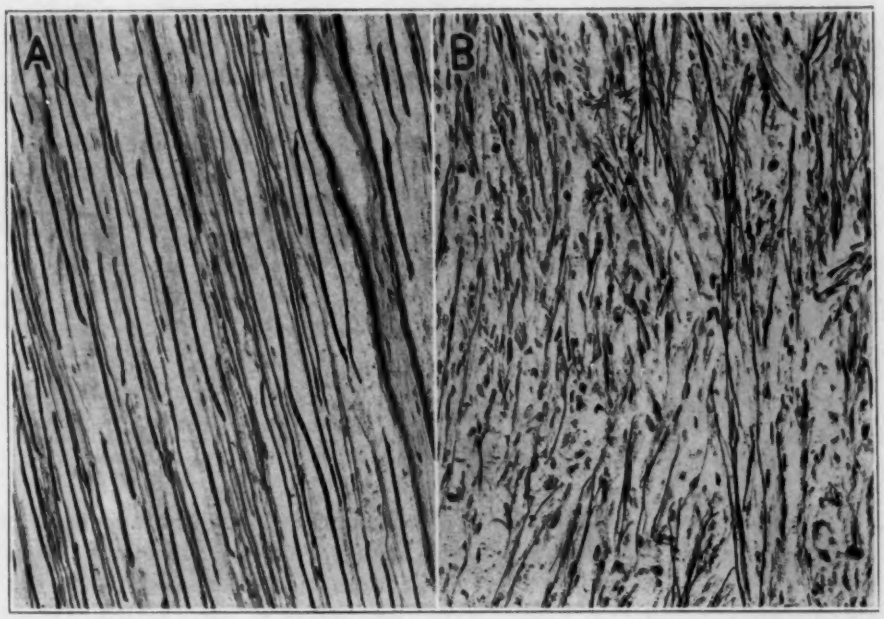


Fig. 4.—*A*, central end of a sciatic nerve twenty-five days after a delayed suture. Fine, pale fibers are sympathetic postganglionic fibers. Silver technic; × 175.

*B*, peripheral stump (near suture line) of the same nerve as that shown in *A*. The central end lies above. There is considerable penetration by new fibers, but regeneration is not as satisfactory as that in a nerve with immediate suture. The new fibers are much smaller than those from which they spring. Silver technic; × 175.

appearance and was evident in all nerves except those treated with sulfanilamide. Curiously, the leukocytes which were immediately adjacent to the drug showed

3. Huber, G. C.: Experimental Observations on Peripheral Nerve Repair, in United States History of the World War: The Medical Department of the United States Army in the World War, Washington, D. C., Government Printing Office, 1927, vol. 11, pt. 1, pp. 1091-1283.

4. Ramón y Cajal, S.: Degeneration and Regeneration of the Nervous System, translated by R. M. May, New York, Oxford University Press, 1928.

5. Nageotte, J.: Sheaths of the Peripheral Nerves: Nerve Degeneration and Regeneration, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 1, sect. 5.

considerable karyorrhexis, indicating a direct, probably chemical, effect. This, however, was a purely local phenomenon and did not appear in any other part of the treated area. There was no observable serous exudate, as reported by Key and Frankel [1]; consequently, the "dry field" postulated by Huber [6] was available for the regenerating nerve.

Other than the production of a foreign body reaction, the local application of the sulfonamide compound had no specific effect on the connective tissue sheaths or other nerve fiber sheaths. The processes of traumatic inflammation and subsequent repair were histologically identical on the treated and on the control side of each animal. This normality after local treatment with sulfonamide compounds agrees with the results of Key, Frankel and Burford [7] and Key and Frankel.[1] It does not, however, agree with the observations of Holmes and Medawar,[8] who noted that proliferation of Schwann cells and invasion of macrophages did not take place normally after the application of 2 Gm. of sulfanilamide to 4 cm. of the sciatic nerve of the rabbit, although there was complete wallerian degeneration of the nerve distal to the site of application of the drug. It should be pointed out that in their experiments the nerve was not cut and that they used an amount

*Absorption of Drug*

| 0.5 Gm. | Number of Observations | Days After Operation * | | | | |
|---|---|---|---|---|---|---|
| | | 2 | 5 | 10 | 15 | 30 |
| Sulfanilamide | 10 | — | — | — | — | — |
| Sulfathiazole | 11 | + | + | + | — | — |
| Sulfapyridine | 10 | + | + | + | + | — |
| Sulfadiazine | 8 | + | + | .. | + | — |
| 0.25 Gm. | | | | | | |
| Sulfanilamide | 6 | .. | — | — | — | — |
| Sulfathiazole | 4 | .. | + (trace) | .. | — | — |
| Sulfapyridine | 6 | .. | + | + | — | — |
| Sulfadiazine | 10 | + | + | + | + | — |

* In this table, — indicates absence of drug; +, presence of drug, and .., no observation.

four times our maximum dose. They did, however, note excellent regeneration in the nerve after sixty days. In view of these facts and of the mechanical obstruction and tissue reaction likely to result after application of large doses of the less soluble sulfonamide drugs (table), it would seem that the dose used should not exceed that needed to insure antisepsis.

Study of this material has led to observations on the pathway taken by newly regenerating fibers. It is generally stated that a massive proliferation of Schwann cells from the distal stump bridges the gap to the central end and that the new fibers then utilize these sheath cells to guide them through the cicatrix and into the old sheath pathways in the distal stump. Recently, Abercrombie and Johnson,[9] Holmes and Young [10] and Young [11] have reaffirmed this view. They used

6. Huber, G. C.: Repair of Peripheral Nerve Injuries, Surg., Gynec. & Obst. **30**:464-471, 1920; footnote 3.

7. Key, J. A.; Frankel, C. J., and Burford, T. H.: The Local Use of Sulfanilamide in Various Tissues, J. Bone & Joint Surg. **22**:952-958, 1940.

8. Holmes, W., and Medawar, P. B.: Local Application of Sulfanilamide to Peripheral Nerves, Lancet **2**:334-335, 1942.

9. Abercrombie, M., and Johnson, M. L.: The Outwandering of Cells in Tissue Culture of Nerves Undergoing Wallerian Degeneration, J. Exper. Biol. **19**:266-283, 1942.

10. Holmes, W., and Young, J. Z.: Nerve Regeneration After Immediate and Delayed Suture, J. Anat. **77**:63-97, 1942.

11. Young, J. Z.: The Functional Repair of Nervous Tissue, Physiol. Rev. **22**:318-374, 1942.

the rabbit as the experimental animal. In our experiments this phenomenon was never observed. We confess to inability to distinguish adequately between the Schwann cells and fibroblasts in the cicatrix (similarly, Ramón y Cajal [4] and Holmes and Young [10] could give no final criteria for distinguishing these two cell types). There is, undoubtedly, a proliferation of Schwann cells in the central and the distal stump, and in most of our specimens it appeared that the Schwann cells from the central end were the ones which passed through the cicatrix around the newly growing fiber, although the growing tip was naked.

On reaching the distal stump, the new fibers take the path of least resistance, which appears to be through the syncytial sheaths of Schwann cells, especially the areas formerly populated by postganglionic axons of the normal nerve, even though many sterile tubes may be nearby (fig. 3 *B*). The disposition agrees with Nageotte's description of regenerating nerve fibers.[12] In some cases, the new fibers appear to be completely outside the sheath cells and in the epineurium. The presence of intratubular phagocytes and degenerating axons and myelin sheaths seems to hinder the penetration of these new fibers in the early stages, but after the debris and phagocytes have been removed, the fibers may utilize old channels. Ramón y Cajal noted that fibers outside the myelin tubes "are most numerous when there are great numbers of sprouts arriving simultaneously at the peripheral stump." [13] Later, in speaking of cases in which the scar is narrow and the cut ends of the nerve are properly oriented, he noted among the more important features "the great number of extratubal conductors, or conductors which are right in the endoneurium." Hannah [14] concluded that fibers reached the peripheral stump six to seven days after hemisection of the rabbit's sciatic nerve and some entered old tubes, while others grew along the endoneurium between the tubes. Nageotte, also, expressed the belief that in a nerve graft (the graft was a nerve killed with weak alcohol) the regenerating fibers find an easy path in the connective tissue stroma of the killed nerve. Our observations tend to confirm the conclusions of these several authors. Holmes and Young,[10] on the other hand, stated the belief that the connective tissue of the endoneurium blocks the new fibers, so that the path usually taken must necessarily be the old sheath tube.

In our transverse sections of the peripheral stump, thirty days after the operation clear spaces were seen around most of the regenerating axons, an observation suggesting the formation of new myelin sheaths (fig. 3 *B*). According to Ramón y Cajal, "the myelin sheath is a late formation, which begins in a few fibers from the twenty-third to the twenty-fifth day after the section, in those peripheral stumps which are separated from the central stump by a narrow scar." [15] Unfortunately, the technic we used did not permit the use of myelin stains, and the narrow spaces noted around the axons may well have been due to shrinkage; however, physiologic observations now being carried out in this laboratory strongly suggest that myelin must be present in many axons of the peripheral stump as early as thirty days after suture.

Nerves with delayed sutures (made five days after section of the nerve) showed the same response as nerves with primary suture. A period of about five days after suture was required for the regenerating fibers to penetrate the suture line and to reach the distal stump. Subsequently the process was normal. Since in

12. Nageotte,[5] pp. 225-226.
13. Ramón y Cajal,[4] p. 235.
14. Hannah, J. A.: Regeneration of Peripheral Nerves: An Experimental Study, Edinburgh M. J. **38**:73-86, 1931.
15. Ramón y Cajal,[4] p. 247.

these nerves the cicatrix was more extensive and, correspondingly, there was greater delay in the penetration of the regenerating axons into the peripheral stump, the conditions for the formation of a schwannian syncytium which would advance from the peripheral to the central stump across the cicatrix were better


Fig. 5.—High power drawing (oil immersion lens), made five days after the second operation, showing growth of regenerating axons through the cicatrix in a nerve with suture. Some of the cells in contact with the growing axons are presumably sheath cells, but they cannot be clearly differentiated from the fibroblasts, especially when the latter are seen on edge. The cytoplasm of the large lamellar fibroblasts contains, or is spread over, fine networks of argyrophil connective tissue fibers. *C* indicates collagenous fibers. Silver technic; × 1,060.

realized. In spite of this, we have been unable to identify the syncytial strands which, according to Nageotte [5] and Marinesco,[16] ensheath the regenerating axons and guide their growth into the peripheral stump.

As already stated, we observed sheath cells migrating along the regenerating axons across the cicatrix. Their intimate contact with the axons permits their identification, but their morphologic characteristics are not different from those of the fibroblasts. Indeed, the characteristic longitudinal striation of the sheath cells in the bands of Büngner is duplicated in cells which are undoubtedly fibroblasts (fig. 5), and when the latter are seen on edge, differentiation of the two types is still more difficult. The presence of fine collagenous fibers (verified in sections stained by the Masson technic and by the method for silver impregnation of the connective tissue) around the growing axons strongly suggests that the latter will follow any available path through the cicatrix. This belief is strengthened by the observation in some of our specimens of regenerating axons within the epineurium, where the presence of strands of Schwann cells is highly problematic.

## SUMMARY AND CONCLUSIONS

1. Sulfanilamide, sulfathiazole, sulfapyridine and sulfadiazine do not appear to exert any chemical influence on the extent and character of nerve regeneration when they are applied at the site of injury to the nerve. If these drugs are not rapidly absorbed, they may offer a mechanical hindrance to the passage of regenerating fibers.

2. The drugs do exert some chemical influence on the phagocytes which surround and invade the drug particles. Such cells are atypical and karyorrhectic, but this phenomenon is purely local and does not extend beyond the immediate neighborhood of the drug.

3. The histologic picture of the sectioned nerve is a typical acute inflammatory reaction (probably due to the operative trauma), followed by reparative fibrosis. The acute reaction subsides after five days, but small groups of inflammatory cells may be seen up to thirty days after the operation. A typical foreign body reaction follows introduction of a sulfonamide compound into the wound, except in the case of sulfanilamide, which is rapidly absorbed.

4. The new nerve fibers are of small and medium size. Thick axons do not regenerate as such, but produce a variable number of small and medium-sized fibers. The new fibers do not penetrate the old myelin sheath pathways but pass down beside them, presumably in a schwannian syncytium or between the sheaths of the endoneurium. A definite schwannoma was not observed.

5. Primary suture offers the best prognosis.

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16. Marinesco, G.: Nouvelles contributions à l'étude de la régénération nerveuse et du neurotropisme, Phil. Tr. Roy. Soc., London, s.B **209**:229-304, 1919.

# ACUTE ARREST OF CEREBRAL CIRCULATION IN MAN

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Numerous investigations have been concerned with the effects of acute arrest of cerebral circulation in animals. The earlier workers [1] studied the effects of ligation of the cerebral arteries. More recently, observations have been made on the effects of temporary occlusion of the chief cerebral arteries [2] and of temporary cessation of the heart beat.[3] Using the method of occlusion of the chief cerebral arteries, Sugar and Gerard [4] measured the survival time for different regions of the cat brain by the persistence of spontaneous action potentials. A careful study of the changes in function and structure of the brain of the cat resulting from temporary occlusion of the pulmonary artery was reported on by Weinberger, Gibbon and Gibbon.[5] These methods involved one or another of the following complications: anesthesia; surgical procedures at the time of arrest of circulation in the brain; incomplete arrest of circulation as a result of failure to occlude the anterior spinal artery; arrest of circulation in vital organs outside the central nervous system, and difficulty of determination of the exact moment of cessation of the heart beat.

For quantitative study a technic was utilized which produced sudden complete arrest of blood flow in the brain of the unanesthetized animal without the per-

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3. Boehm, R.: Ueber Wiederbelebung nach Vergiftungen und Asphyxie, Arch. f. exper. Path. u. Pharmakol. **8**:68, 1877. Batelli, F.: Le rétablissement des fonctions du coeur et du système nerveux central après l'anémie totale, J. de physiol. et de path. gén. **2**:443, 1900. Crile, G., and Dolley, D. H.: On the Effects of Complete Anemia of the Central Nervous System in Dogs Resuscitated After Relative Death, J. Exper. Med. **10**:782, 1908. Heymans, C.; Bouckaert, J. J.; Jourdan, F.; Nowak, S. J. G., and Farber, S.: Survival and Revival of Nerve Centers Following Acute Anemia, Arch. Neurol. & Psychiat. **38**:304 (Aug.) 1937.

4. Sugar, O., and Gerard, R. W.: Anoxia and Brain Potentials, J. Neurophysiol. **1**:558, 1938.

5. (*a*) Weinberger, L. M.; Gibbon, M. H., and Gibbon, J. H., Jr.: Temporary Arrest of the Circulation to the Central Nervous System: I. Physiologic Effects, Arch. Neurol. & Psychiat. **43**:615 (April) 1940. (*b*) II. Pathologic Effects, ibid. **43**:961 (May) 1940.

formance of a surgical procedure at the time and without deprivation of other organs of blood or oxygen. This was accomplished [6] by the use of a cervical pressure cuff in dogs at a pressure of 600 mm. of mercury following a preliminary cervical laminectomy. With this method, the corneal reflex disappeared within ten seconds and spontaneous respiration ceased in twenty to thirty seconds. The essential basis for this rapid loss of function was lack of oxygen for the neurons. In normal adult dogs of either sex, periods of arrest of circulation in the brain of six minutes or less, while producing severe functional changes for a time, were invariably followed by apparently complete functional recovery. On the other hand, arrest of circulation in the brain for longer than six minutes uniformly resulted in permanent coma, due to functional decortication. Damage to the brain was sharply localized in specific sensitive areas and was confined to the nerve cells.[7] The course of functional recovery was essentially the same as had been reported in cases of acute arrest of cerebral circulation in man by hanging.[8] The brain of the very young animal was much more resistant to arrest of blood flow than that of the adult [9] while pregnancy or lactation increased the sensitivity of the brain to temporary arrest of circulation.[10]

Relatively little study has been made of the effects of acute arrest of blood flow in the human brain. The most significant contributions in this field have been those of the Harvard group: namely, the studies on the hypersensitive carotid sinus reflex and carotid sinus syncope,[11] on the relation of the oxygen content of blood in the internal jugular vein to loss of consciousness [12] and on the electroencephalographic pattern associated with carotid sinus syncope.[13] Other investigators [14] have described the clinical syndrome produced by short periods of acute anoxia induced by breathing gas mixtures of low oxygen content. Of considerable interest

6. (*a*) Kabat, H., and Dennis, C.: Decerebration in the Dog by Complete Temporary Anemia of the Brain, Proc. Soc. Exper. Biol. & Med. **38**:864, 1938. (*b*) Kabat, H.; Dennis, C., and Baker, A. B.: Recovery of Function Following Arrest of the Brain Circulation, Am. J. Physiol. **132**:737, 1941.

7. (*a*) Kabat, H., and Schadewald, M.: The Relative Susceptibility of the Synaptic Terminals and of the Perikaryon to Arrest of the Circulation of the Brain, Am. J. Path. **17**:833, 1941. (*b*) Kabat, H., and Grenell, R. G.: Specificity of Localization of Neuronal Injury Following Arrest of Brain Circulation, Anat. Rec. **82**:33, 1942.

8. Strauss, H.: Strangulationsfolgen und Hirnstamm, Ztschr. f. d. ges. Neurol. u. Psychiat. **131**:363, 1931. Salinger, F., and Jacobsohn, H.: Psychische Störung nach Strangulationsversuch, ibid. **110**:372, 1927. Kabat, Dennis and Baker.[6b]

9. Kabat, H.: The Greater Resistance of Very Young Animals to Arrest of the Brain Circulation, Am. J. Physiol. **130**:588, 1940.

10. Kabat, H.: The Influence of Pregnancy and Lactation on the Susceptibility to Arrest of the Brain Circulation, Proc. Soc. Exper. Biol. & Med. **44**:23, 1940.

11. (*a*) Weiss, S., and Baker, J. P.: The Carotid Sinus in Health and Disease: Its Role in the Causation of Fainting and Convulsions, Medicine **12**:297, 1933. (*b*) Ferris, E. B., Jr.; Capps, R. B., and Weiss, S.: Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions, ibid. **14**:377, 1935.

12. Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: (*a*) Relationship of Unconsciousness to Cerebral Blood Flow and to Anoxemia, Arch. Neurol. & Psychiat. **34**:1001, 1935; (*b*) The Relationship in Man of Cerebral Activity to Blood Flow and to Blood Constituents, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:277, 1938.

13. Forster, F. M.; Roseman, E., and Gibbs, F. A.: Electroencephalogram Accompanying Hyperactive Carotid Sinus Reflex and Orthostatic Syncope, Arch. Neurol. & Psychiat. **48**: 957 (Dec.) 1942.

14. Fraser, R., and Reitmann, F.: A Clinical Study of the Effects of Short Periods of Severe Anoxia with Special Reference to the Mechanism of Action of Cardiazol Shock, J. Neurol. & Psychiat. **2**:125, 1939.

are the studies on recovery from attempted suicide by hanging [15] and resuscitation after cardiac arrest.[16]

All these investigations on acute arrest of circulation in the human brain were limited almost entirely to patients with various disorders, such as hypersensitive carotid sinus reflex, orthostatic hypotension and Stokes-Adams disease. Many of these patients were in the older age group and suffered from arteriosclerosis, hypertension or heart disease. The experiments were difficult to control, and much variation was noted, which limited the accuracy of quantitative observations. Furthermore, there is reason to believe [13] that the syncope resulting from stimulation of a hypersensitive carotid sinus reflex is complex and bears a closer relation to an epileptiform seizure than to syncope from cerebral anemia.

In order to study the effect of acute cerebral anoxia in man, a new technic was devised, which used the Kabat-Rossen-Anderson apparatus. This procedure is essentially an adaptation to the human subject of the method devised by one of us [6] for producing arrest of cerebral circulation by means of a cervical pressure cuff. Acute arrest of circulation in the human brain was studied in 11 schizophrenic patients and in 126 normal young male subjects. No deleterious effects were observed from repeated tests on these subjects.

## ANATOMY AND PHYSIOLOGY

Arterial blood is supplied to the human brain chiefly through the internal carotid and the vertebral arteries, but to some extent by anastomotic connections of branches of the external carotid and the subclavian artery. In addition, some blood reaches the brain through the small spinal arteries.

The common carotid artery is readily occluded by external cervical pressure, blood flow to the brain through the internal carotid artery and branches of the external carotid artery being thereby eliminated. The ascending branches of the subclavian artery, with the exception of the vertebral artery, are also readily occluded by a circular cervical pressure cuff.

The vertebral artery is a branch of the first part of the subclavian artery. In the lower portion of the neck, the first part of the vertebral artery runs upward and backward between the scalenus anticus and the longus colli muscle to enter the foramen in the transverse process of the sixth cervical vertebra. The second part of the vertebral artery passes upward, entering the series of foramens in the transverse processes of the vertebrae from the sixth cervical to the atlas. The third part of the vertebral artery enters the skull and joins the vertebral artery of the opposite side at the base of the brain to form the basilar artery. It is impossible to occlude the third part of the vertebral artery by cervical pressure. The second portion is difficult to occlude by external pressure because the artery can be compressed only where it passes through muscles between the transverse processes. The first portion of the vertebral artery may be occluded readily by external pressure in the lower third of the neck, since it is surrounded by muscle.

The only arterial inflow to the brain which cannot be occluded by a cervical pressure cuff lies within the vertebral canal and passes up with the spinal cord, protected by bone. These vessels, the anterior spinal arteries, join the vertebral arteries just before the junction of the latter to form the basilar artery. These

15. Bingel, A., and Hampel, E.: Spättod nach Erhängen. Beitrag zur Klinik und Anatomie der Kreislaufstörungen im Gehirn, Ztschr. f. d. ges. Neurol. u. Psychiat. **149**:640, 1934. Footnote 8.

16. von Novak, E.: Ueber die intrakardiale Injektion, Deutsche Ztschr. f. Chir. **250**:310, 1938.

vessels are relatively minute in man. Since the chief source of supply for these vessels in the cervical region is the vertebral arteries, occlusion of the latter should also greatly reduce blood flow to the brain in the anterior spinal arteries. Furthermore, with stasis of blood in the brain resulting from occlusion of both arteries and veins, it seems unlikely that any quantity of blood could flow from the lower end of the brain stem through vessels filled with blood to supply oxygen to the sensitive cerebral cortex.

The venous return from the brain is chiefly through the internal jugular, the external jugular and the cervicalis profunda vein. These veins are surrounded by muscle and are readily occluded by a cervical pressure cuff.

The neurons in the brain are the cells of the body most sensitive to anoxia. There appear to be specific differences in sensitivity to anoxia in different centers of the brain. The great sensitivity to anoxia and hypoglycemia of cerebral neurons is due to their high metabolic rate, their failure to use stored glycogen for energy and their dependence on circulating dextrose, their low anaerobic glycolysis and their highly specialized character. The pronounced loss of function of the human brain resulting from brief periods of arrest of circulation appears to be due primarily to lack of oxygen rather than to lack of dextrose or accumulation of metabolites.

## METHOD

The Kabat-Rossen-Anderson apparatus has been designed to induce temporary arrest of circulation in the human brain without affecting the respiratory tract. This is accomplished by means of a specially designed inflatable cervical pressure cuff, held down to the lower third of the neck. The pressure in the cuff rises to 600 mm. of mercury within one-eighth second. The subject himself, as well as the physician, controls the deflation of the cuff, which can be accomplished within a fraction of a second. The apparatus allows full observation of the sitting subject at all times for accurate recording. The reactions of the subject may readily be recorded by means of devices such as the electrocardiograph and the electroencephalograph. The sudden inflation of the cuff to a high pressure causes occlusion of the vessels to the brain before the next heart beat, so that engorgement of the cerebral vessels is prevented.

The pressure cuff has been improved in the course of this investigation, so that the earlier experiments on the schizophrenic patients and normal subjects are valuable chiefly for their qualitative observations.

The procedure has been applied repeatedly to the same subjects, with no injurious effects. Periods of acute arrest of cerebral circulation for as long as one hundred seconds appear to be well tolerated and are followed by rapid and uneventful recovery.

## RESULTS

I. *Clinical Effects of Brief Periods of Acute Arrest of Cerebral Circulation in Normal Subjects.*—The characteristic reactions resulting from acute arrest of the circulation in the brain for five to ten seconds were fixation of the eyeballs, blurring of vision, constriction of the visual fields, loss of consciousness and anoxic convulsions. This response occurred with great rapidity and was uniform from subject to subject. Our procedure was to release the pressure in the cuff simultaneously with loss of consciousness by the subject. Recovery occurred quickly in every case, and the procedure was demonstrated to be free from danger. All subjects could stand, walk out of the room and go about their work within one or two minutes after the procedure, and no later effects were observed. In addition to the reactions already mentioned, some subjects showed turning up of the eyeballs and tingling or shooting pains in the extremities.

A. Eyes: Fixation of eyes: The earliest and most constant objective reaction to acute anoxia of the human brain was fixation of the eyes. This was tested by having the subject move his eyes rhythmically from side to side in the horizontal plane while they followed the moving finger of the examiner or a freely swinging

pendulum. In the usual subject, after five or six seconds of cerebral anoxia, the eyes fixed suddenly in the midline and the subject was incapable of moving the eyes, although he was still conscious (loss of consciousness occurred one-half to one second after fixation of the eyes). The subject stated afterward that he tried to follow the examiner's finger and could see it moving, but was unable to move his eyes. The great sensitivity to anoxia of the centers for voluntary motion of the eyes has been demonstrated by McFarland, Knehr and Berens [17] in studies on the effects of breathing gas mixtures low in oxygen on ocular movements associated with reading. It appears likely that this disturbance of function of extraocular muscles is dependent on derangement of cortical rather than of subcortical activity.

Turning up of the eyes: In some subjects, about one-half second after fixation of the eyes in the midline, the eyeballs suddenly turned upward, the reaction coinciding with loss of consciousness and immediately preceding the anoxic convulsion. These subjects were usually sensitive to cerebral anoxia and had a more severe convulsive seizure than usual.

Subjective ocular symptoms: Before loss of consciousness, many subjects experienced rapid narrowing of the field of vision, blurring of vision, with the field of vision becoming gray, and, finally, complete loss of vision. A number of subjects stated that they were unable to see but could still hear and were conscious. Occasionally subjects reported that they experienced positive or negative scotomas, such as light or dark streaks or spots or twinkling lights progressing inward from the periphery of the visual field. The last-mentioned phenomenon was observed particularly by a subject who suffered from migraine. The great sensitivity of the visual cortex to arrest of circulation has been observed in animal experiments,[18] as well as in studies on anoxia in human subjects.[19]

B. Anoxic Convulsions: These seizures were of a generalized tonic and clonic type; they were usually relatively mild and rarely continued more than six to eight seconds. No twitching of individual muscles was observed. There was no excessive salivation, and no subject fell from his chair, bit his tongue or suffered any injury. The convulsion was preceded by loss of consciousness, and the subject usually remained unconscious throughout the seizure and had no memory of it. Some subjects regained consciousness during the latter part of the seizure and reported that they felt themselves shaking but were unable to control it.

A point of considerable interest is the fact that the seizure occurred after release of pressure in the cuff, and rarely or never during the acute cerebral anoxia. Restoration of blood flow simultaneously with fixation of the eyes often aborted a seizure, while continuation of cerebral anoxia for one or two seconds after fixation of eyes resulted in a more severe and prolonged seizure. There was considerable variation in the severity and duration of the convulsions in different subjects and in the same subject at different times.

C. Paresthesias: These took the form of numbness, tingling and shooting pains, which were noted during the arrest of cerebral circulation and rapidly disappeared after restoration of blood flow. The paresthesias varied greatly in intensity, in some cases being relatively mild and in others consisting of severe shooting pains down the arm or leg, much like an electric shock, of sufficient intensity to force

17. McFarland, R. A.; Knehr, G. A., and Berens, C.: The Effects of Anoxemia on Ocular Movements While Reading, Am. J. Ophth. **20**:1204, 1937.

18. Weinberger and others.[5a] Kabat and Grenell.[7b]

19. Gellhorn, E.: Effect of Oxygen Lack, Variations in Carbon Dioxide Content of Inspired Air and Hyperpnea on Visual Intensity Discrimination, Am. J. Physiol. **115**:679, 1936.

the subject to release the pressure in the cuff. Only a little more than half the subjects reported paresthesias during arrest of blood flow in the brain, and paresthesias did not invariably occur in the same subject on repeated trials. The paresthesias were noted most frequently in the hands, arms, head and face, but were also observed in the lower extremities, back, shoulders, chest and abdomen (visceral), and in a number of instances all over the body. The paresthesias appeared earlier than other reactions, several seconds before loss of consciousness. It is likely that these subjective sensory phenomena are the result of stimulation of the neurons of the postcentral gyrus, as an early phase of acute anoxia. Comparably brief periods of arrest of circulation in an extremity failed to produce paresthesias.

D. Loss of Consciousness: Usually within one second after fixation of the eyes the subject appeared dazed, his eyelids drooped, his head dropped down on his chest and he slumped in his chair. If the examiner counted the seconds aloud, the subject could recall only the count up to five or six, at which time he also appeared to lose consciousness. Consciousness was also tested by having the subject respond to the flashing of a green light by pressing a button which rang a buzzer. This response also disappeared slightly before the subject appeared to lose consciousness.

Although the subject was instructed to remove his finger from the jet as soon as he felt like it, and thereby release the pressure in the cuff, he failed to do so, despite loss of consciousness and an anoxic convulsion. The subject's hand thus appeared to "freeze" in that position and became incapable of voluntary or involuntary relaxation. It was therefore almost invariably necessary for the examiner to take the responsibility of releasing the pressure. Most subjects did not realize that they were holding on to the jet. Some stated that they did not feel like bothering to release the pressure. Others stated that they tried to remove the finger from the jet but were incapable of the movement.

A variety of mental symptoms were observed on the subject's returning to consciousness. The symptoms were brief and did not last more than fifteen to twenty seconds. The subject was dazed and appeared confused, usually having a foolish smile on his face. Some appeared temporarily excited and euphoric. Some insisted that they did not lose consciousness, although they had no memory of the convulsion and failed to respond to the flashing light. Others appeared frightened and tense for a few seconds and then suddenly relaxed, smiled and appeared normal. Some subjects did not respond to the flashing light for many seconds after restoration of circulation in the head but suddenly responded when ordered to do so by the examiner. They stated that they saw the light, knew they were supposed to respond by pressing the button, but did not care, did not want to bother and had no will or inclination to move. Schwab [20] has reported that the reaction to visual stimuli was absent or the reaction time was prolonged in petit mal attacks and that attacks were terminated more rapidly by auditory stimuli than by other kinds.

E. Electroencephalogram and Electrocardiogram: [21] The electroencephalographic changes corresponded to the records obtained from patients with orthostatic hypotension.[22] The sudden appearance of large slow waves was closely correlated with fixation of the eyes or loss of consciousness. No increase in

20. Schwab, R. S.: The Influence of Visual and Auditory Stimuli on the Electroencephalographic Tracing of Petit Mal, Am. J. Psychiat. **97**:1301, 1941.

21. Records were made under the supervision of Dr. E. J. Baldes.

22. Lennox, Gibbs and Gibbs.[12b] Forster and others.[13]

frequency was noted, an observation which supports the contention of Forster, Roseman and Gibbs [13] that the increased frequency of brain waves in cases of carotid sinus syncope of the central type indicates that cerebral anemia is not a major factor in this type of syncope.

Electrocardiographic changes were minimal, with slight sinus slowing in some subjects and no change in others.

II. *Effects of Prolonged Arrest of Cerebral Circulation in Patients with Mental Disease.*—Arrest of cerebral circulation for as long as one hundred seconds was carried out on 11 schizophrenic patients. These studies were made early with a technic which often failed to produce complete arrest of cerebral blood flow, so that the results were variable. However, qualitative changes resulting from these long periods of arrest of blood flow are of interest. In these tests the subject was supine.

Cerebral circulation has been arrested by means of cervical pressure for as long as one hundred seconds. All subjects regained consciousness within thirty to forty seconds after restoration of circulation in the brain and were able to walk from the room within two minutes after the procedure. Late effects have never been observed. During the arrest of circulation, loss of consciousness, convulsions, marked cyanosis, involuntary urination and defecation, bradycardia, dilatation of the pupils and changes in reflexes were recorded. Respiration was increased in rate and amplitude but continued throughout the procedure. After restoration of blood flow there was pronounced flushing of the face and consciousness soon returned, followed by interesting temporary changes in the behavior of the patient.

A. Pulse and Blood Pressure: In the first twenty to thirty seconds after arrest of blood flow in the brain there was no decided change in the pulse, a slight increase or decrease in rate being observed. As the arrest of circulation was continued, a notable slowing of the heart frequently occurred, sometimes to less than 50 per cent of the original rate. This bradycardia was readily prevented by administration of atropine sulfate and was apparently the result of direct stimulation of the cardioinhibitory center of the vagus nerve in the medulla by arrest of blood flow.[23] After administration of atropine arrest of cerebral circulation usually increased the heart rate.

The blood pressure was recorded immediately before arrest of cerebral circulation and immediately after restoration of the blood flow. Usually there was a moderate rise or fall of the systolic pressure, not exceeding 15 per cent, with less evident changes in the diastolic pressure.

B. Reflexes: Corneal reflex: In 150 trials the time of disappearance (survival time) of the corneal reflex was measured as accurately as possible. In the earlier studies, the corneal reflex either persisted throughout the procedure or disappeared as late as fifty to seventy-five seconds after inflation of the cuff. With improvement of technic and more complete occlusion of the cervical vessels, the survival time of the corneal reflex declined sharply and became more constant in repeated trials, so that the later trials may represent complete arrest of circulation in the brain.

In 1 patient the corneal reflex was observed to disappear six seconds after inflation of the cuff. In other trials with the same subject the survival time of the corneal reflex was recorded at eight and ten seconds. In another patient, on repeated trials, the survival times of the corneal reflex were seven, seven and one-

23. Kabat, H.: The Cardio-Accelerator Fibers in the Vagus Nerve of the Dog, Am. J. Physiol. **128**:246, 1940.

half, nine, nine, ten and ten seconds. In a third patient the corneal reflex was observed to disappear in ten seconds, and in a fourth subject, in eleven seconds. Since all of these studies were made before the apparatus was fully perfected, there is still some question concerning the completeness of arrest of blood flow in the brain in these trials. Therefore one may conclude that the center for the corneal reflex in man is extremely sensitive to arrest of cerebral circulation and that the survival time of the corneal reflex is undoubtedly less than ten seconds. This corresponds to the observation of Kabat, Dennis and Baker [6b] that the wink reflex in the dog, produced by touching the inner canthus of the eye, disappears within ten seconds after complete arrest of the circulation in the brain. The centers in the brain stem concerned with respiration, blood pressure and heart rate are evidently much more resistant to anoxia than is the reflex center for the corneal reflex. Furthermore, the areas of the cerebral cortex which inhibit the pathologic reflexes and maintain the abdominal reflexes also appear to show greater resistance to anoxia than the center for the corneal reflex.

The time for recovery of the corneal reflex was variable, depending on the duration of arrest of blood flow, as well as on the completeness of vascular occlusion. After one hundred seconds of cerebral anoxia, with a survival time of twenty seconds for the corneal reflex, several subjects had recovery times of twelve to twenty seconds. After thirty seconds of arrest of blood flow, with survival times less than ten seconds, the time for recovery of the corneal reflex varied from four to seven seconds.

In 1 patient the cochleopalpebral reflex (wink produced by a loud noise close to the ear) persisted seven seconds and, after twenty-five seconds of arrest of blood flow, was restored in nine seconds.

Abdominal reflex: This reflex is diminished or absent during prolonged arrest of the cerebral circulation. It was difficult to determine accurately the survival time of this reflex, but in several trials absence of the reflex was noted after ten, forty and fifty seconds. In 1 instance the abdominal reflex disappeared before the corneal reflex. Usually the abdominal reflex had disappeared before the appearance of pathologic reflexes. The abdominal reflex was still absent long after the restoration of the corneal reflex. After arrest of circulation for one hundred seconds, the abdominal reflex returned in two to four minutes after restoration of blood flow in the brain.

It is well known that frequently the earliest objective diagnostic sign of a tumor in the frontal lobe is the decrease or disappearance of the abdominal reflexes. The usual explanation is that the tumor first encroaches on the cerebral center for the abdominal reflexes because this area is more rostral in the brain than are the areas for the pathologic reflexes, such as the Babinski sign. This is pure hypothesis, since there is no conclusive evidence on the problem of localization of the center for the abdominal reflex in the cerebral cortex.[24] An alternative explanation suggests itself from the foregoing observations, namely, that the encroaching tumor, resulting in ischemia, first produces decrease or abolition of the abdominal reflex before the ischemia has affected the function of the cortical neurons concerned with pathologic reflexes, because of the greater sensitivity of the center for the abdominal reflex to decreased blood flow.

Pathologic reflexes: Various pathologic reflexes were observed to appear during prolonged arrest of the cerebral circulation and to disappear soon after restoration of the blood flow. The appearance of these reflexes was variable, but

24. Brock, S.: The Basis of Clinical Neurology, Baltimore, William Wood & Company, 1937, p. 63.

was usually preceded by decrease or disappearance of the abdominal reflexes. The Babinski, Hoffmann and Rossolimo signs, and occasionally the Gordon reflex, were tested for immediately before occlusion of the cervical vessels and repeatedly during and after arrest of the cerebral circulation. In 6 of 10 patients studied, the Rossolimo sign could be elicited during arrest of circulation to the brain, while the Babinski and Gordon reflexes could not be obtained and the Hoffmann reflex was elicited only occasionally. In 2 subjects the first appearance of the Rossolimo sign was recorded at fifty seconds after occlusion of the cervical vessels, and the reflex was noted to disappear within a few seconds after release of pressure in the cuff. In 8 patients, despite the disappearance of the abdominal reflexes and the appearance of other pathologic reflexes, tests for the Babinski and the Gordon sign gave uniformly negative results during the cerebral stasis. A Babinski sign was observed during arrest of cerebral circulation in 2 subjects, but in other trials on the same patients they could not be elicited throughout the procedure. In several patients a questionable Babinski sign was noted. The Hoffmann sign was not elicited in 6 patients and was obtained during arrest of circulation to the brain in 3 patients. In 4 subjects who presented a Rossolimo sign the Hoffmann reflex was consistently absent. In 2 patients, on the other hand, arrest of cerebral blood flow resulted in the appearance of a Hoffmann sign, while the Rossolimo reflex could not be obtained.

From these observations one may conclude that in man the cortical area concerned with the Babinski and Gordon reflexes, presumably area 4 of Brodmann, is more resistant to acute anoxia than is the cortical area for the Rossolimo and Hoffmann reflexes, presumably area 6 of Brodmann.[25] In most subjects area 6 for the foot (Rossolimo sign) was more sensitive to anoxia than area 6 for the hand (Hoffmann sign). In some subjects, however, area 6 for the hand was the more sensitive. The pathologic changes in area 6 were more severe than those observed in area 4 after relatively prolonged arrest (nineteen minutes) of the cerebral circulation in dogs.[26]

Involuntary urination and defecation: Seven of the 11 patients subjected to relatively prolonged arrest of the cerebral circulation showed reflex urination fairly consistently on repeated trials. Urination was noted fifteen to forty seconds after occlusion of the vessels supplying the brain. Two of these patients showed involuntary defecation thirty seconds after arrest of circulation to the brain.

C. Eyes: A number of observations were made on the eyes of patients during relatively prolonged cerebral anoxia. In 7 patients the eyegrounds were examined by means of the ophthalmoscope by Dr. Clyde Cabot. During the arrest of cerebral circulation there was observed moderate dilatation of the retinal veins, which became darker, the color corresponding to the degree of cyanosis present; the optic disks also became somewhat darker, while no change was noted in the retinal arteries. The eyegrounds were restored to normal within a few seconds after release of pressure in the cuff. Moderate dilatation of the pupils was observed twelve to twenty seconds after beginning of the arrest of cerebral circulation.

A characteristic feature of the response to acute arrest of the cerebral circulation in all patients was conjugate deviation of the eyes. This lasted only from a few to ten seconds and was frequently associated with the tonic phase of an epileptiform seizure. The conjugate deviation was consistently to the left and upward in 3 patients and consistently to the right and upward in 4 patients. In 1 sub-

25. Fulton, J. F., and Viets, H. R.: Upper Motor Neuron Lesions, J. A. M. A. **104**:357 (Feb. 2) 1935.

26. Kabat, H.: Unpublished observations. Kabat and Grenell.[7b]

ject the head was rotated temporarily to the side to which the eyes deviated. After this brief conjugate deviation, the eyes gradually returned to the midposition or rotated slowly to the opposite side. Usually the conjugate deviation of the eyes was observed soon after the disappearance of the corneal reflex. With relatively complete arrest of cerebral circulation conjugate deviation of the eyes was recorded in ten to twenty seconds.

D. Epileptiform Convulsions: The seizures which occurred during and after arrest of the cerebral circulation were atypical grand mal convulsions. They were brief and relatively mild and showed repeated alternating tonic and clonic phases. The clonic phase rarely lasted longer than ten seconds and was not always generalized. The patient was always unconscious during the seizure and had no memory of it. There was no increase in salivation. Consciousness was recovered rapidly, and no injury or later symptoms were ever noted.

Although the convulsions varied a good deal, one usually noted a tonic phase beginning about fifteen seconds after occlusion of the cervical arteries, followed at twenty to twenty-five seconds by a brief clonic phase. The first tonic phase of the seizure was frequently accompanied by conjugate deviation of the eyes. With relatively complete arrest of cerebral circulation for one hundred seconds, the mild seizure was over thirty to forty seconds after beginning of the arrest, and the patient was relaxed during the remainder of the period of cerebral anoxia; restoration of blood flow resulted in a brief tonic and clonic convulsion. In some patients alternating tonic and clonic phases continued throughout the period of circulatory arrest. One patient showed, after restoration of cerebral blood flow, apparent catatonia and a peculiar flexor rigidity of the left hand, which differed from carpal spasm.

E. Psychiatric Observations: No significant improvement in the psychiatric status of the schizophrenic patients was noted after repeated and relatively prolonged periods of arrest of cerebral circulation. In some subjects behavior was more nearly normal for several minutes after recovery of consciousness following prolonged cerebral anoxia. Two catatonic patients who had not spoken for a long time responded rationally to questions for several minutes after recovery. In several patients characteristic mannerisms disappeared during this period. The failure to demonstrate therapeutic effects from the procedure may perhaps be related to the fact that all the patients had suffered from schizophrenia for longer than five years, that some were greatly deteriorated and that all had failed to improve with insulin and metrazol therapy.

III. *Quantitative Studies on Normal Subjects.*—The exact times for fixation of the eyes and for loss and recovery of consciousness during brief periods of arrest of cerebral circulation were studied in normal volunteers. These determinations were carried out with the improved pressure cuff and apparatus, which produced complete arrest of circulation to the brain. The subject sat facing the examiner and was instructed to move the eyes rhythmically in the horizontal plane while they followed the moving finger of the examiner or a swinging pendulum. He was also instructed to respond to the flashing of a green light by pressing a button which sounded a buzzer. On some subjects electroencephalograms were obtained and the changes correlated with the clinical observations. Either the subject or the examiner could release the pressure cuff at any desired time. The usual procedure was for the examiner to restore cerebral blood flow simultaneously with loss of consciousness of the subject, so that the circulation to the brain was usually arrested for less than ten seconds.

The subjects were 126 apparently normal male volunteers, ranging in age from 17 to 31 years. Eighty-two of the men were inmates of the Minnesota State Reformatory, St. Cloud, Minn., and ranged in age from 17 to 25 years. The other subjects were at the Minnesota State Prison in Stillwater, Minn., and ranged in age from 21 to 31 years. Repeated tests were carried out on 85 of these subjects. Similar tests were also performed on the investigators and their associates.

The time from occlusion of the cervical vessels to fixation of the eyes in the midline could be measured objectively within one-half second by means of a stop-

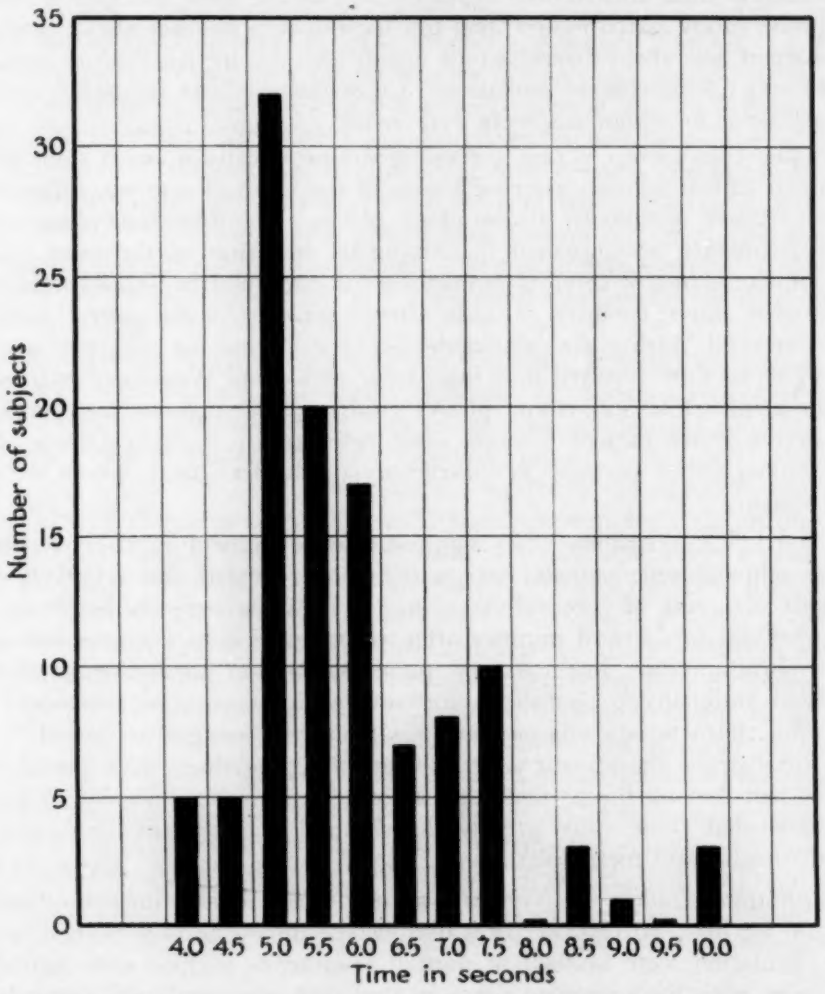


Fig. 1.—Distribution curve for time to fixation of the eyes during acute arrest of cerebral circulation in 111 normal young men.

watch. At this time the subject was still apparently conscious. A distribution curve for fixation time for different normal subjects is shown in figure 1. It is apparent from this graph that almost half the subjects tested showed fixation of the eyes five or five and a half seconds after initiation of cerebral anoxia. The relative constancy of fixation time on repeated tests on the same subject, illustrated in the table, suggests that cerebral blood flow was usually arrested completely by the KRA apparatus. Failure to respond to the light-buzzer test coincided in time with fixation of the eyes, while apparent loss of consciousness, characterized by sudden

slumping of the head and body, occurred about one second after fixation of the eyes. The delta wave usually appeared in the electroencephalogram about one second after fixation of the eyes.

The recovery time was measured as the time from fixation of the eyes to restoration of the response to the light-buzzer test. The time to fixation of the eyes, as a measure of resistance of the cerebral neurons to anoxia, might be expected to correlate with the time of recovery. Also, one would expect correlation of recovery of cerebral function and duration of arrest of circulation. Analysis of the data shows that there is no significant correlation between time of recovery and time of fixation or, within narrow limits, between time of recovery and duration of cerebral anoxia. The distribution curve for recovery times for 28 normal

*Consistency of Time * to Fixation of Eyes on Repeated Tests on Different Days*

| Subject No. | First Test | Second Test | Third Test | Fourth Test | Subject No. | First Test | Second Test | Third Test | Fourth Test |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 5 | 5 | 5 | 7½ | 38 | 6 | 5 | .. | .. |
| 2 | 6 | 5 | 5½ | 5½ | 39 | 7 | 5½ | .. | .. |
| 3 | 5 | 7 | 5 | 9½ | 40 | 7 | 7 | 6½ | .. |
| 4 | 10 | 12 | .. | .. | 41 | 5½ | 5½ | 5½ | .. |
| 5 | 7 | 7½ | 6½ | .. | 42 | 5½ | 5½ | .. | .. |
| 6 | 5 | 5 | 5½ | .. | 43 | 5½ | 5 | .. | .. |
| 7 | 5 | 4½ | .. | .. | 44 | 4 | 5 | 5 | 5 |
| 8 | 4 | 4 | 4½ | .. | 45 | 5 | 5 | .. | .. |
| 9 | 5 | 5 | 5½ | .. | 46 | 6½ | 5 | 5 | .. |
| 10 | 10 | 10 | .. | .. | 47 | 7 | 5½ | 5½ | .. |
| 11 | 5 | 7½ | 9½ | .. | 48 | 5 | 5 | .. | .. |
| 12 | 4½ | 5 | 5½ | .. | 49 | 6 | 6½ | 5 | .. |
| 13 | 6 | 6 | 7 | .. | 50 | 5 | 5½ | 5 | .. |
| 14 | 3 | 4½ | 4½ | 5 | 51 | 6 | 6½ | 6 | .. |
| 15 | 5 | 5½ | .. | .. | 52 | 5½ | 5½ | 5 | 5 |
| 16 | 10 | 10½ | .. | .. | 53 | 6½ | 8½ | 7 | .. |
| 17 | 7 | 7½ | 8 | .. | 54 | 5 | 5½ | 5½ | .. |
| 18 | 5 | 5 | 6 | .. | 55 | 3 | 5 | 5 | .. |
| 19 | 5 | 5 | .. | .. | 56 | 6½ | 7 | 7 | .. |
| 20 | 4 | 4 | .. | .. | 57 | 7 | 6 | 6½ | .. |
| 21 | 6 | 5½ | 5 | 7½ | 58 | 6 | 6½ | 6 | .. |
| 22 | 5 | 8 | .. | .. | 59 | 7½ | 7½ | 7½ | 8 |
| 23 | 3 | 5½ | 5 | .. | 60 | 5½ | 6 | 5½ | .. |
| 24 | 6 | 5½ | 5½ | .. | 61 | 4½ | 5½ | 5½ | 5½ |
| 25 | 6 | 5 | .. | .. | 62 | 6 | 6 | 5½ | .. |
| 26 | 6 | 6 | 5 | 5½ | 63 | 7 | 6½ | 6 | 6 |
| 27 | 5 | 5 | 5 | .. | 64 | 5 | 6½ | 5½ | 6 |
| 28 | 5 | 6 | 5 | .. | 65 | 5 | 5½ | 5 | 5½ |
| 29 | 5½ | 5½ | .. | .. | 66 | 4½ | 5 | .. | .. |
| 30 | 4 | 5 | 5 | 6 | 67 | 7 | 5½ | .. | .. |
| 31 | 4½ | 5 | .. | .. | 68 | 8½ | 7½ | .. | .. |
| 32 | 4½ | 5 | 5 | 5½ | 69 | 7 | 7½ | 6 | .. |
| 33 | 4½ | 5 | 5½ | .. | 70 | 6½ | 6 | .. | .. |
| 34 | 7½ | 8 | 7 | .. | 71 | 4½ | 5 | .. | .. |
| 35 | 4 | 4 | .. | .. | 72 | 6 | 7 | .. | .. |
| 36 | 4½ | 5 | 4¾ | .. | 73 | 6 | 6 | .. | .. |
| 37 | 5 | 6 | .. | .. | 74 | 6 | 5½ | .. | .. |

* The fixation times are expressed in seconds.

subjects is shown in figure 2. The results of the first test were not used in determining the recovery time for these subjects because this test frequently showed prolongation of this period, due most likely to such factors as unfamiliarity with the test and apparatus and emotional reactions. The importance of such factors was emphasized by the observation that 1 subject had a prolonged recovery time on an occasion on which he became depressed and worried. On the other hand, his working until midnight and having the test early the next morning, before breakfast, had no influence on the recovery time. In tests for recovery time by this method, complex factors, chiefly psychologic, play a role as important as the sensitivity of the cerebral neurons to acute anoxia. The range of variations in recovery time on repeated tests on the same subject was much greater than that for the time to fixation of the eyes.

IV. *Effects of Preengorgement and Administration of Members of the Vitamin B Complex on the Response of Normal Subjects to Acute Arrest of Cerebral Circulation.*—The effects of preengorgement on the response to acute cerebral anoxia were investigated in 7 normal subjects, aged from 26 to 30 years. The preengorgement was produced by applying a pressure of 80 to 85 mm. of mercury in the cervical cuff for fifteen to eighteen seconds. This procedure obstructed the venous return without affecting the arterial inflow and presumably increased the concentration of carbon dioxide and other metabolites in the brain tissues. Within one second after release of the preengorgement pressure, the pressure in the cuff was raised suddenly to 600 mm. of mercury, with production of acute arrest of the cerebral circulation. Each subject was studied without preengorgement in three tests. Then, for the following three tests, preengorgement was produced,

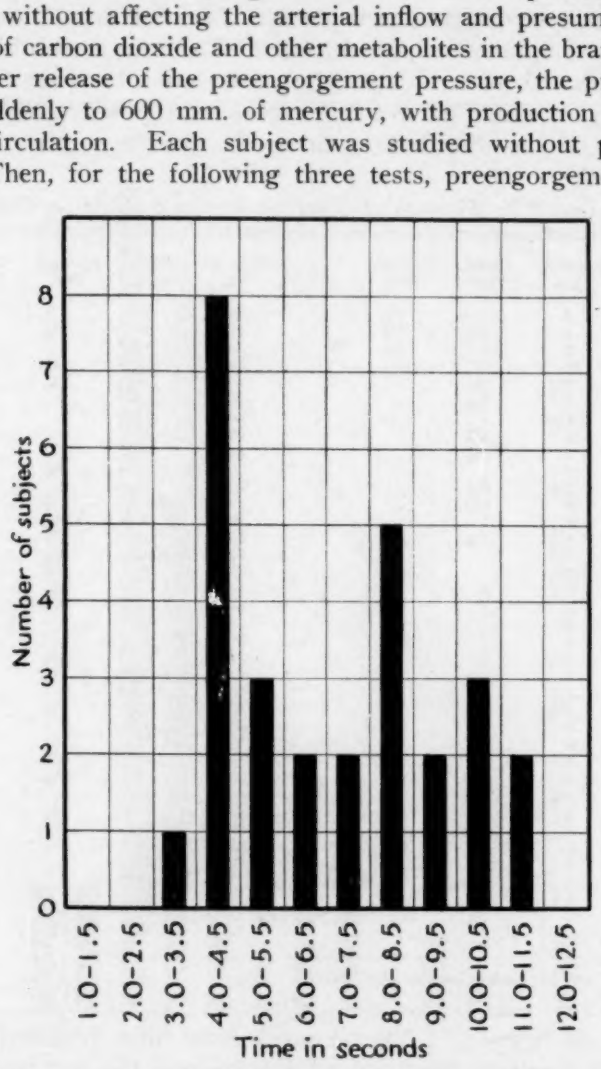


Fig. 2.—Distribution curve for time of recovery of the light-buzzer response following acute arrest of circulation to the brain in 28 normal young men. The graph shows average values on repeated tests (first test omitted).

as previously outlined. For the final test only acute cerebral anoxia was produced, without preengorgement. The duration of arrest of cerebral circulation was the same in all tests on the same person.

Preengorgement had no effect on the time to fixation of the eyes. The average fixation time without preengorgement was five and ninety-two hundredths seconds, and the average fixation time with preengorgement was five and nine-tenths seconds for the same subjects. This suggests that preengorgement fails to influence the sensitivity of cerebral neurons to anoxia. On the other hand, as illustrated in

figure 3, the average time for recovery of the light-buzzer response was reduced significantly by preengorgement. The final test on January 27, without preengorgement, showed a much longer recovery time than the three previous tests, with preengorgement. While there was a tendency for recovery to become more rapid with greater experience, this cannot explain the results with preengorgement illustrated in figure 3. Analysis of recovery times for individual subjects with and without preengorgement shows an even more striking acceleration of recovery with preengorgement. Perhaps the more rapid recovery may be related to improved circulation and utilization of oxygen in the brain after restoration of blood flow, as a result of increased concentration of carbon dioxide.

The influence of B complex vitamins in large doses on the time to fixation of the eyes and on time of recovery following occlusion of the cerebral blood supply was investigated in 9 subjects. Each subject was given daily oral doses of 200 mg. of nicotinic acid amide and 30 mg. of thiamine hydrochloride from January 13 to January 19. In addition, 3 of the subjects ingested 100 mg. of riboflavin

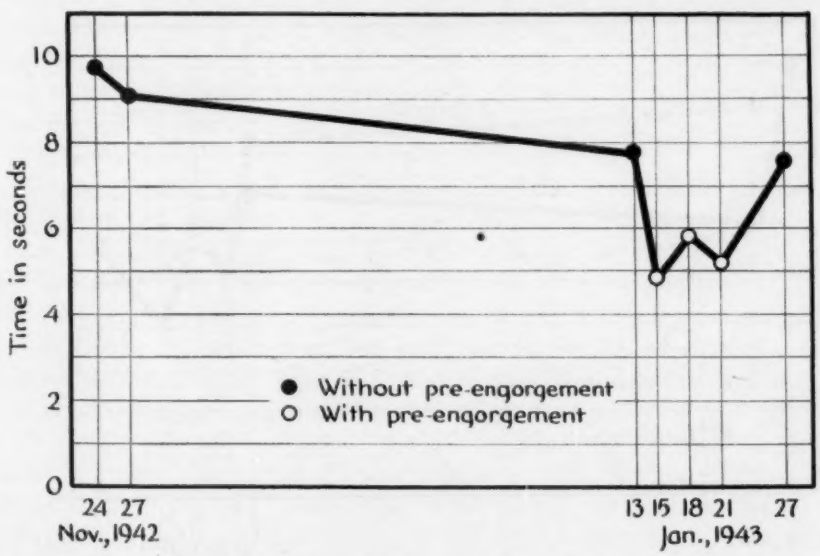


Fig. 3.—Effect of preengorgement on recovery time following acute arrest of cerebral circulation. The graph shows the average time of recovery for 7 normal young men on repeated tests.

from January 18 to January 26. The results on time to fixation of the eyes showed no significant change resulting from administration of the B vitamins: The average fixation time before vitamin B therapy was five and seventy-six hundredths seconds, and that during vitamin therapy was five and nine-tenths seconds. The effects on time of recovery of the light-buzzer response showed a moderate acceleration of recovery from cerebral anoxia with nicotinic acid amide and thiamine, either given alone or followed by riboflavin (fig. 4). In view of the small number of subjects and the complex nature of the test, these results should be considered only suggestive.

## COMMENT

This is the first controlled investigation on the effects of acute arrest of the circulation to the human brain. Other methods, such as the study of patients with hypersensitive carotid sinus reflex [27] or the induction of orthostatic hypotension by posture or administration of nitrites,[13] cannot be controlled for comparison with

27. Footnote 11. Forster and others.[18]

the performance of normal subjects. Furthermore, the major factor in carotid sinus syncope is not usually arrest of circulation to the brain.[18]

One is impressed by the remarkable sensitivity of the function of the human brain to acute anoxia. The greatest number of subjects showed fixation of the eyes after cerebral anoxia for five to five and a half seconds and became unconscious after six to six and a half seconds. In studying syncope in patients with hypersensitive carotid sinus reflex, Weiss and Baker [11a] noted that after complete arrest of the heart consciousness was usually lost in eight seconds and regularly lost within twelve seconds. In some of their cases loss of consciousness occurred in five or six seconds. To explain such rapid loss of consciousness, they stated: "It is probable that in the latter cases, in addition to changes in systemic circulation, direct alterations in cerebral blood vessels also played a role." The data presented in the present report make such an assumption unnecessary. The somewhat longer maintenance of consciousness following cardiac asystole than with our procedure may be explained on the basis that arrest of the heart fails to arrest cerebral

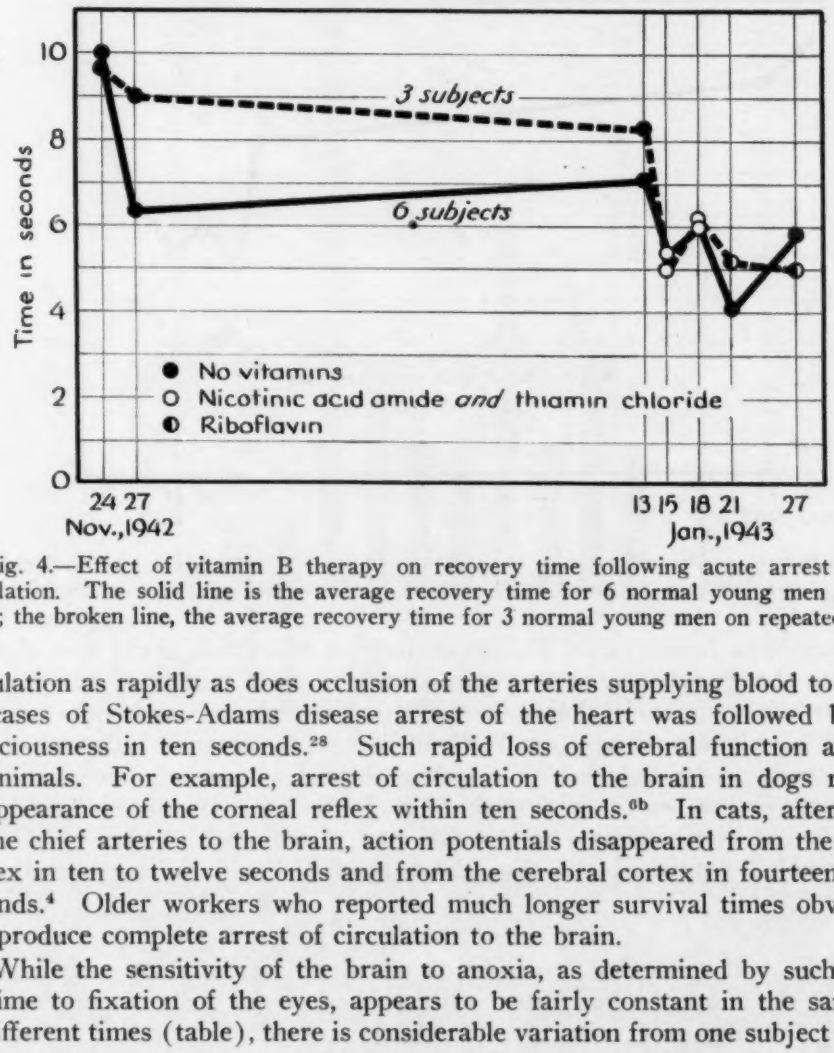


Fig. 4.—Effect of vitamin B therapy on recovery time following acute arrest of cerebral circulation. The solid line is the average recovery time for 6 normal young men on repeated tests; the broken line, the average recovery time for 3 normal young men on repeated tests.

circulation as rapidly as does occlusion of the arteries supplying blood to the brain. In cases of Stokes-Adams disease arrest of the heart was followed by loss of consciousness in ten seconds.[28] Such rapid loss of cerebral function also occurs in animals. For example, arrest of circulation to the brain in dogs resulted in disappearance of the corneal reflex within ten seconds.[6b] In cats, after occlusion of the chief arteries to the brain, action potentials disappeared from the cerebellar cortex in ten to twelve seconds and from the cerebral cortex in fourteen to fifteen seconds.[4] Older workers who reported much longer survival times obviously did not produce complete arrest of circulation to the brain.

While the sensitivity of the brain to anoxia, as determined by such measures as time to fixation of the eyes, appears to be fairly constant in the same person at different times (table), there is considerable variation from one subject to another

28. Penfield, W.: The Circulation of the Epileptic Brain, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:605, 1938.

(fig. 1). These individual differences in sensitivity to acute cerebral anoxia do not appear to be the result of incomplete arrest of the circulation to the brain. The constancy of response of the same person on repeated tests, as well as the demonstration that opacity of the ear does not increase during arrest of the circulation to the head by the KRA apparatus, indicates that circulation to the brain is arrested completely by this method.

The only factor besides circulation which would play a role in determining the sensitivity to cerebral anoxia is the metabolism of the neurons. Quantitative differences in utilization of oxygen by different brains could result in corresponding differences in the rapidity of loss of function following occlusion of the arterial supply to the brain. Differences in cerebral metabolism have usually been regarded as of no significance in studies on oxygen utilization of the human brain by arteriovenous oxygen measurements. Differences among individual subjects and differences associated with various diseases with respect to removal of oxygen from the blood by the brain have been ascribed entirely to differences in cerebral blood flow.[29] The assumption that cerebral metabolism is constant led Williams and Lennox [29a] to the dubious conclusion that 4 patients with high intracranial pressure who were in deep coma, from which they could not be roused, had "an increased rather than a decreased cerebral blood flow." The authors came to this conclusion by observing that the arteriovenous oxygen differences were somewhat lower than normal.

The range of variations in time to fixation of the eyes and to loss of consciousness in the studies presented in this paper, despite complete arrest of cerebral circulation, strongly suggests that the metabolism of the human brain varies from one person to another, even in healthy males ranging in age from 17 to 31 years. It is logical to expect individual variations in an organ as complex in structure and function as the brain, when it is well known that simpler systems show variations of considerable magnitude. Furthermore, similar individual variations have been noted in arteriovenous oxygen differences in the brain. Williams and Lennox [29a] reported a range of arteriovenous oxygen differences with various cerebral conditions as follows: high intracranial pressure, 4.33 to 9.83 volumes per cent; hypertension, 3.49 to 9.45 volumes per cent, and cerebral arteriosclerosis, 4.9 to 10.2 volumes per cent. Ferris [29b] reported in his patients a range of arteriovenous oxygen differences from 3.8 to 9.2 volumes per cent. Of greatest interest in this connection is the recent report of Gibbs and associates [30] on cerebral arteriovenous oxygen differences in 50 normal men from 18 to 29 years of age. They found an average arteriovenous oxygen difference of 6.7 volumes per cent, with a range from 4.5 to 8.5 volumes per cent. It is more than a coincidence that the distribution curve plotted from the data on arteriovenous oxygen differences reported by Gibbs and associates [30] corresponds so closely to the distribution curve for time to fixation of the eyes following arrest of circulation to the brain (compare figures 5 and 1).

Little interest has been shown in this wide range of individual variations in arteriovenous oxygen differences in the human brain. Usually it has been assumed that such variations represent quantitative differences in cerebral blood flow. However, it is questionable whether the cerebral blood flow varies so widely in normal young men under ordinary conditions. Indeed, students of cerebral blood

29. (*a*) Williams, D., and Lennox, W. G.: The Cerebral Blood Flow in Arterial Hypertension, Arteriosclerosis and High Intracranial Pressure, Quart. J. Med. **8**:185, 1939. (*b*) Ferris, E. B.: The Effect of High Intracranial Venous Pressure upon the Cerebral Circulation and Its Relation to Cerebral Symptoms, J. Clin. Investigation **18**:19, 1939.

30. Gibbs, E. L.; Lennox, W. G.; Nims, L. F., and Gibbs, F. A.: Arterial and Cerebral Venous Blood: Arterio-Venous Differences in Man, J. Biol. Chem. **144**:325, 1942.

flow have placed great emphasis on its constancy. Thus, Lennox,[31] from studies of gases in the blood of the internal jugular vein, the cubital vein and the femoral vein, was impressed with the constancy of blood flow in the human brain. In 17 hospitalized patients, Ferris,[32] measuring the relative intracranial blood flow by a plethysmographic method, found a variation of from 118 to 171 cc. per minute. This is a range of variation considerably smaller than Gibbs and his associates observed for arteriovenous oxygen differences in normal healthy young men.

Under normal conditions the mean blood pressure is the most important factor in determination of the cerebral blood flow. "The systemic arterial pressure is more important in its effect on the total cerebral blood flow than any of the other factors (intracerebral or extracerebral)."[33] The mean blood pressure in men younger than 40 without signs of cardiovascular disease varied from 76 to 98 mm. of mercury.[34] Other workers, by direct determination of the mean blood pressure

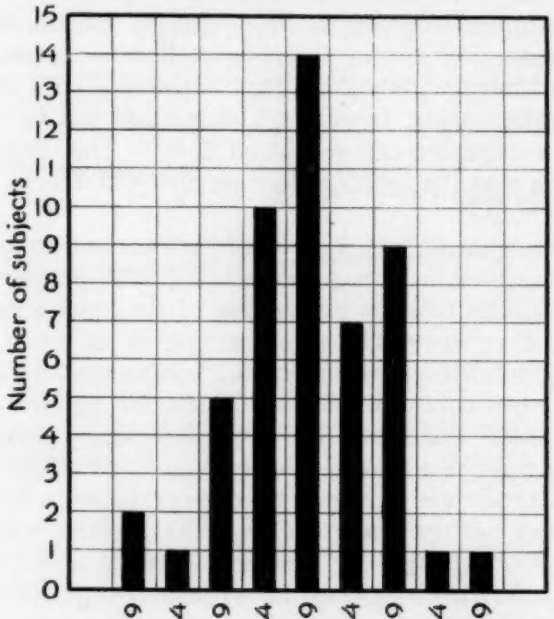


Fig. 5.—Distribution curve for cerebral arteriovenous oxygen differences for 50 normal young men, plotted from the table of Gibbs, Lennox, Nims and Gibbs (J. Biol. Chem. **144**:325, 1942).

by puncturing the femoral artery of subjects lying down, but not under basal conditions, have reported a range of variations from 70 to 95 mm. of mercury.[35]

31. Lennox, W. G.: Constancy of Cerebral Blood Flow, Arch. Neurol. & Psychiat. **36**:375 (Aug.) 1936.

32. Ferris, E. B., Jr.: Objective Measurement of Relative Intracranial Blood Flow in Man, Arch. Neurol. & Psychiat. **46**:377 (Sept.) 1941.

33. Forbes, H. S.: Physiologic Regulation of the Cerebral Circulation, Arch. Neurol. & Psychiat. **43**:804 (April) 1940.

34. von Bonsdorff, B.: Zur Methodik der Blutdruckmessung, Acta med. Scandinav. **51**:7, 1932.

35. Laubry, C.; Beerens, J., and van Bogaert, A.: Tension moyenne intra-artérielle normale chez l'homme, Compt. rend. Soc. de biol. **113**:238, 1933.

Individual variation in cerebral blood flow may be expected to be small, since its chief determining factor, the mean arterial pressure, shows such a small range of variation. One may conclude, therefore, that the individual variation in cerebral arteriovenous oxygen differences in normal young men and the variation in sensitivity to cerebral anoxia noted by us may best be accounted for by variations in metabolism of the normal human brain.

From our data and the observations reported by other workers, it has been possible to calculate the average oxygen consumption of the brain in normal young men. From the data of Gibbs and associates [30] one may calculate that capillary blood in the brain would contain on the average 16.25 volumes per cent of oxygen. Assuming that the average weight of the brain is 1,360 Gm. and that 7 per cent of this weight is blood, from which oxygen can diffuse into the tissue,[36] one obtains a figure of 95 cc. of blood in the brain, trapped by the KRA apparatus. This quantity of blood contains 15.44 cc. of oxygen. Lennox, Gibbs and Gibbs.[12a] demonstrated that man becomes unconscious if the oxygen saturation in the internal jugular venous blood is 24 per cent or less. At a saturation of 24 per cent, the blood in the brain would contain 4.75 cc. of oxygen; when this is subtracted from 15.44, one obtains a remainder of 10.69 cc. of oxygen. This 10.69 cc. of oxygen must be used up in the period from initiation of arrest of circulation to the brain to the exact moment of loss of consciousness. The average time to loss of consciousness in our normal subjects was six and eight-tenths seconds. One thus arrives at an average volume for oxygen utilization of 1.56 cc. per second for the human brain, or a total of 4,140 cu. mm. of oxygen per gram per hour. According to Gerard,[36] the most reliable figure for total oxygen utilization in the animal brain is that of Schmidt,[37] who obtained a value of 4,500 cu. mm. per gram per hour for the dog brain. Gerard [36] recorded a value for oxygen utilization by the cat cortex of 4,000 to 5,000 cu. mm. per gram per hour. Our calculation of the amount of oxygen utilized by the human brain is probably a rough approximation to the average figure, but it suggests that the total cerebral metabolism in man does not differ greatly per unit weight of tissue from that of the dog or cat.

If the average human brain uses 1.56 cc. of oxygen per second, it requires 93.60 cc. of oxygen per minute. Since from each 100 cc. of blood passing through the brain 6.7 cc. of oxygen is removed,[30] the average blood flow through the brain which would satisfy this oxygen requirement is about 1,400 cc. per minute. This is close to 100 cc. per hundred grams of brain tissue per minute. Actual measurement of intracranial blood flow in man by Ferris [32] gave an average of 132 cc. per minute. He stated:

> Since the displacement rates for control subjects have ranged from about 125 to 150 cc. per minute, it is probable that the total intracranial blood flow of such subjects does not exceed 250 to 400 cc. per minute.

Such a small blood flow as Ferris postulated would fail by a wide margin to satisfy the oxygen requirement of the brain. The technic of Ferris, as well as the thermostromuhr of Gibbs, Gibbs and Lennox,[38] is of value in determining changes in blood flow produced by various agents, but gives little information concerning the exact quantitative measurement of the total blood flow. In dogs the average

36. Gerard, R. W.: Brain Metabolism and Circulation, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:316, 1938.

37. Schmidt, C. F.: The Influence of Cerebral Blood Flow on Respiration: II. The Gaseous Metabolism of the Brain, Am. J. Physiol. **84**:223, 1928.

38. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: The Cerebral Blood Flow in Man as Influenced by Adrenalin, Caffein, Amyl Nitrite and Histamine, Am. Heart J. **10**:916, 1935.

blood flow recorded was 130 cc. per hundred grams of brain per minute.[39] In the rabbit Jensen [40] calculated a blood flow of 136 cc. and Winterstein [41] a blood flow of 60 cc. per hundred grams of brain per minute. In a recent investigation on the monkey, Dumke and Schmidt [42] observed a rate of cerebral blood flow of 86 cc. per hundred grams of brain per minute. It is probable that an average rate of cerebral blood flow of 100 cc. per hundred grams per minute is the correct value for various mammals, including man.

Since the cardiac output in man at rest is about 4 to 4.5 liters per minute, the blood flow through the brain is approximately one third of the total output of the left ventricle. This is remarkable since the brain represents only about 2 per cent of the body weight.

## CONCLUSIONS

A new method, using the KRA apparatus, has been devised to produce complete arrest of the cerebral circulation in man.

Acute arrest of the cerebral circulation in normal young men results in fixation of the eyes, tingling, constriction of the visual fields, loss of consciousness and, immediately after restoration of blood flow, a brief, mild tonic and clonic seizure.

The average time from arrest of cerebral circulation to loss of consciousness in normal young men is six and eight-tenths seconds. This coincides with the sudden appearance of the delta wave in the electroencephalogram. One second before loss of consciousness one observes fixation of the eyes in the midline.

The time for recovery of the light-buzzer response depends on personality factors and does not correlate with sensitivity to acute anoxia. The time of recovery appears to be decreased by preengorgement and administration of large doses of the B vitamins.

Arrest of the circulation to the human brain for one hundred seconds may be followed by rapid recovery of consciousness and no objective evidence of injury. The corneal reflex may disappear in less than ten seconds. The abdominal reflex disappears, and the Rossolimo and Hoffmann reflexes often become positive during acute cerebral anoxia, while the Babinski reflex is not obtained.

Considerable individual variation has been noted in sensitivity of normal young men to acute arrest of circulation to the brain. This variation is apparently due to differences in cerebral metabolism in different persons. The resistance to acute anoxia is fairly constant for the same person at different times.

Calculations based on this investigation give figures for oxygen utilization of the human brain of 1.56 cc. per second, or 4,140 cu. mm. per gram per hour. This corresponds closely to figures for total brain metabolism reported for the dog and cat. To supply the brain with oxygen, the blood flow through that organ must average 1,400 cc. per minute, or about 100 cc. per hundred grams of brain weight per minute. At rest, the brain receives about one third of the output of the left ventricle, per minute, although it represents only 2 per cent of the body weight.

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39. Gollwitzer-Meier, K., and Eckhardt, P.: Weitere Untersuchungen über den Nerveneinfluss auf die Hirndurchblutung, Arch. f. exper. Path. u. Pharmakol. **177**:501, 1935.

40. Jensen, P.: Ueber die Blutversorgung des Gehirn, Arch. f. d. ges. Physiol. **103**:171, 1904.

41. Winterstein, H.: Ueber den Blutkreislauf im Kaninchenhirn, Arch. f. d. ges. Physiol. **235**:377, 1935.

42. Dumke, P. R., and Schmidt, C. F.: Quantitative Measurements of Cerebral Flow in the Macaque Monkey, Am. J. Physiol. **138**:421, 1943.

# CHANGES IN THE ELECTROENCEPHALOGRAM FOLLOWING METRAZOL SHOCK THERAPY

## A QUANTITATIVE STUDY

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Several recent reports (Davis and Sulzbach [1]; Finley and Lesko [2]; Polatin, Strauss and Altman [3]; Levy, Serota and Grinker [4]) have indicated permanent or semipermanent changes in the electroencephalogram following metrazol shock therapy. In the main these authors seem to agree that a large number of metrazol-induced convulsions will produce electrocortical potentials of high amplitude and very slow frequency. Until a critical number of convulsions is reached, which varies from patient to patient, there is no change in the record beyond a temporary one that is attributable to the convulsion itself (Goodwin, Kerr and Lawson [5]; Strauss and Rahm [6]). Polatin, Strauss and Altman [3] reported, for instance, that in all their cases there was a return to the preconvulsion electroencephalogram within a few hours after the administration of metrazol, until some number of convulsions, up to 12, was reached, after which severe and more than transient mental changes occurred; as the mental symptoms reversed, the electroencephalogram again returned to normal. Levy, Serota and Grinker,[4] in contrast, reported 1 case with a conspicuous slow abnormality in the electroencephalogram after three metrazol convulsions and 2 cases with a similar abnormality after five convulsions. In several of their cases increase in the alpha rhythm (presumably a more "normal" record) followed shock therapy, an observation in accordance with the results of Finley and Lesko.[2] While Polatin, Strauss and Altman [3] and Levy, Serota and Grinker [4] suggested that such electroencephalographic abnormalities as appear may

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1. Davis, P. A., and Sulzbach, W.: Changes in the Electroencephalogram During Metrazol Therapy, Arch. Neurol. & Psychiat. **43**:341 (Feb.) 1940.

2. Finley, K. H., and Lesko, J. M.: EEG Studies of Nine Cases with Major Psychoses Receiving Metrazol, Am. J. Psychiat. **98**:185, 1941.

3. Polatin, P.; Strauss, H., and Altman, L. L.: Transient Organic and Mental Reactions During Shock Therapy of the Psychoses, Psychiatric Quart. **14**:457, 1940.

4. Levy, N. A.; Serota, H. M., and Grinker, R. R.: Disturbances in Brain Function Following Convulsive Shock Therapy: Electroencephalographic and Clinical Studies, Arch. Neurol. & Psychiat. **47**:1009 (June) 1942.

5. Goodwin, J. E.; Kerr, W. K., and Lawson, F. L.: Bioelectric Responses in Metrazol and Insulin Shock, Am. J. Psychiat. **96**:1389, 1940.

6. Strauss, H., and Rahm, W. E., Jr.: The Effect of Metrazol Injections on the Electroencephalogram, Psychiatric Quart. **14**:43, 1940.

be transient, Davis and Sulzbach [1] and Finley and Lesko [2] indicated that in certain instances the alterations may be permanent.[7]

The present observations were made in an attempt to quantify electroencephalographic abnormalities induced by metrazol convulsions, so that the following questions could be answered: Is there any relation between the number of convulsions and the degree of abnormality of the electroencephalogram? Is there any relation between slow activity in the preconvulsion and that in the postconvulsion electroencephalogram? Are the changes in the electroencephalogram more prominent in some areas of the cortex than in others?

## METHOD

Twenty patients with depressions, selected for treatment with metrazol shock, were utilized in this study. Since the electroencephalographic recording for these patients required adaptation to several clinical regimens, records were obtained for 11 patients before and after therapy and for 9 patients after therapy only.

Cortical potentials were recorded by means of three matched amplifiers and a Grass three element ink-writing oscillograph. The recording speed was 3 cm. per second. The leads were solder disks cemented to the scalp with collodion; neutral leads were attached in parallel to the lobes of the ears. With all patients the left occipital, the left motor and the left frontal area were used for analysis.

The records were analyzed as follows: Four samples, each 1 meter long (representing a run of thirty-three and three-tenths seconds), were selected from a continuous record of at least fifteen minutes' duration, and the number of centimeters in each sample occupied by potentials having a duration of 5 mm. or greater (i. e., a frequency of 6 per second or less) was determined; this value was taken as the percentage of slow activity; the average for the four samples was secured, and the latter value was used as the slow activity index for the record. In similar samples of record the per cent time alpha (8.5 to 12.5 per second activity) was computed; this was the alpha index. In certain instances it was technically impossible to secure an analyzable record from the motor and frontal areas, owing to excessive sweating, undiminishable muscular tension or blinking.

## RESULTS

Table 1 presents the data pertaining to measurements of slow and alpha activity before and after metrazol shock therapy, and table 2, measurements of slow activity after shock therapy for patients for whom no preshock measurements were available.

The first measurements to be considered are those of slow activity before and after treatment. Records for patient 1 (table 1) were obtained before and after a first course of two convulsions; there was a sharp increase in the slow activity index for the left motor area in a record secured five days after the last convulsion; on the eleventh day after the last convulsion, there was no notable change, but thirty-seven days afterward the percentage of slow activity was strikingly reduced and probably was within the range of normal variation. This patient was readmitted two hundred and ten days (seven months) later. At this time the slow activity index had increased above the thirty-seven day value and had returned to approximately the five day value with respect to the slow activity index for the left frontal area. In the left occipital and left motor areas the indexes were well above their pretreatment levels.

Patient 2 (table 1) gave evidence of a somewhat similar process of decline in the slow activity index. Records from the left occipital and left motor areas before metrazol therapy showed fairly high indexes. After six convulsions there was a

7. "Permanent" as used here is of course a relative term; the longest published period of observation after treatment is sixteen and a half months.

slight increase in the slow activity index in the left motor area, the index for the left occipital area fluctuating downward somewhat. The patient was readmitted one hundred and fifty days after the last of these six convulsions and received

TABLE 1.—*Per Cent Time Slow and Alpha Activity* in the Electroencephalograms of Patients with Depressions, Before and After Metrazol Shock Therapy*

| Patient No. | Record Taken Before or After Treatment | Area: Left Occipital S. I.† | Left Occipital A. I.† | Left Motor S. I. | Left Motor A. I. | Left Frontal S. I. | Left Frontal A. I. | Number of Convulsions | Number of Days After Last Convulsion |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Before | 2.4 | 20.3 | 2.8 | 6.2 | .... | .... | | |
| | After | 3.3 | 36.5 | 12.7 | 18.0 | 17.3 | 9.9 | 2 | 5 |
| | After | 3.8 | 9.1 | 12.5 | 9.1 | 20.5 | 5.6 | .. | 11 |
| | After | 1.3 | 22.4 | 4.3 | 14.5 | 2.8 | 13.3 | .. | 37 |
| | After | 9.2 | 15.9 | 7.1 | 5.5 | 17.0 | 6.1 | .. | 210 |
| 2 | Before | 14.3 | 7.3 | 18.3 | 7.8 | .... | .... | | |
| | After | 11.3 | 51.1 | 23.6 | 27.7 | 13.9 | .... | 6 | 11 |
| | After (before 2d series) | 19.8 | 26.2 | 25.9 | 8.3 | 17.5 | 7.8 | .. | 150 |
| | After 2d series | 16.8 | 45.4 | 19.2 | 35.6 | 13.7 | 40.1 | 5 (total 11) | 5 |
| 3 | Before | 0.6 | 82.9 | 1.4 | 22.7 | 0.2 | 20.1 | | |
| | After (before 2d series) | 13.4 | 61.1 | 1.7 | 26.7 | 2.1 | 32.6 | 3 | 270 |
| | After 2d series | 11.6 | 91.7 | 2.8 | 55.7 | 5.1 | 66.8 | 20 | 1 |
| 4 | Before | 4.6 | .... | 8.1 | .... | 16.1 | .... | | |
| | After | 19.3 | .... | 35.6 | .... | 43.5 | .... | 6 | 4 |
| 5 | Before | 3.6 | 59.5 | 6.5 | 21.2 | 6.0 | 11.3 | | |
| | After | 11.3 | 34.2 | 22.4 | 19.5 | 12.1 | 9.4 | 5 | 3 |
| 6 | Before | 7.5 | 27.5 | 3.1 | 15.2 | 5.5 | 16.0 | | |
| | After | 6.0 | 27.6 | 10.5 | 24.1 | 13.1 | 24.6 | 6 | 10 |
| 7 | Before | 0.9 | 95.0 | 3.1 | 21.4 | 1.8 | 25.3 | | |
| | After | 12.6 | 34.6 | 15.1 | 11.5 | 17.2 | 11.9 | 6 | 5 |
| 8 | Before | 1.4 | 79.9 | 2.2 | 59.9 | 1.5 | 43.3 | | |
| | After | 3.5 | 49.5 | 3.5 | 12.5 | 10.4 | 11.1 | 5 | 2 |
| 9 | Before | 5.6 | 23.0 | .... | 8.8 | .... | 2.8 | | |
| | After | 19.2 | 30.5 | .... | 19.8 | .... | 12.0 | 5 | 4 |
| 10 | Before | 8.9 | 21.4 | 2.3 | 24.9 | 5.1 | 17.5 | | |
| | After | 4.2 | 37.5 | 9.3 | 35.8 | 6.1 | 27.7 | 4 | 12 |
| 11 | Before | 18.8 | 18.3 | 34.1 | 6.4 | 16.6 | 14.0 | | |
| | After | 15.7 | 46.4 | 22.1 | 31.5 | 22.6 | 29.9 | 4 | 7 |

* By slow activity is meant frequencies of from 1 to 6 per second; by alpha activity, frequencies of from 8.5 to 12.5 per second.
† S. I. indicates slow activity index; A. I., alpha index.

TABLE 2.—*Percentage of Slow (1 to 6 per Sec.) Activity in the Electroencephalogram After Metrazol Shock Therapy*

| Patient No. | Area: Left Occipital | Left Motor | Left Frontal | Number of Convulsions | Number of Days After Last Convulsion |
|---|---|---|---|---|---|
| 1 | 35.4 | 46.0 | 47.1 | 6 | 1 |
| 2 | 65.9 | 79.4 | 79.3 | 5 | 3 |
| 3 | 6.2 | 7.8 | 9.4 | 1 | 3 |
| 4 | 7.5 | 11.6 | 10.3 | 10 | 7 |
| 5 | 14.0 | 25.1 | 28.6 | 10 | 7 |
| 6 | 14.1 | 20.9 | 19.8 | 14 | 8 |
| 7* | 6.8 | 12.7 | 29.8 | 9 | 8 |
| 8 | 2.8 | 9.6 | 14.8 | 5 | 10 |
| 9 | 13.8 | 18.8 | 30.1 | 10 | 13 |
| 7* | 2.9 | 12.7 | 4.4 | 9 | 17 |

* Values for this patient were entered twice; the second entry was made from the record taken nine days after the first.

a second series of treatments, of five convulsive doses of metrazol. At this time there was an increase in the slow activity index for each of the three areas. Five days after the second course of treatments (or after a total of eleven convulsions)

the indexes for these areas had decreased, the values for the left occipital and left motor areas nearing the original levels.

Records for patient 3 (table 1) obtained before institution of therapy exhibited very low slow activity indexes for the three areas. This patient was discharged before a follow-up record could be obtained, but he was readmitted for further treatment two hundred and seventy days after the last convulsion. The slow activity index for the left occipital area was much higher than prior to treatment but did not exceed the probable normal variation for the other areas. One day after the second course of treatment, in which twenty convulsions were induced, records were again secured; there was in all likelihood an insignificant variation.

The remaining 8 patients showed similar individual variations in the response of the electroencephalograms to convulsive therapy. On the basis of these data, the following statements may be made: In general, there is an increase in the slow activity index after a series of convulsions induced by metrazol. This is, in general, greater in the motor and frontal leads than in the occipital lead. (In the normal electroencephalogram, Gibbs [8] reported a similar gradient from the anterior to the posterior region.) Statistical justification of these generalizations is found in table 3, in which are presented the mean slow activity index and the range of index values for each area, before and after treatment, and the *t* values

TABLE 3.—*Mean and Range of Slow Activity Indexes in Records Taken Before and After Treatment*

| | Left Occipital Area | Left Motor Area | Left Frontal Area |
|---|---|---|---|
| Before therapy | 6.2 (0.6-18.8) | 8.2 (1.4-34.1) | 6.6 (0.2-16.1) |
| After therapy | 10.9 (3.3-19.3) | 15.7 (1.7-35.6) | 15.9 (2.1-43.5) |
| Difference | 4.7 | 7.5 | 9.3 |
| Number of experiments | 11 | 10 | 8 |
| t | .. | 2.54 | 3.02 |
| Level of confidence | Not significant | 5% | 2% |

(Lindquist [9]) which indicate the significance of the difference between the pretreatment and the post-treatment value, for all patients in table 1, on whom preconvulsion and postconvulsion data were obtained.

The anterior cortical areas were significantly changed after convulsive therapy. The increase in the slow activity index for the frontal area could be attributed to chance in only 2, and that for the motor area in only 5, of 100 experiments. The alteration in the occipital area, however, could not be regarded as significant; statistically, the difference may be regarded as due to chance.

When the preconvulsion and postconvulsion values for the slow activity indexes were ranked, it was found that there was some degree of correlation between them. Rank-order correlations were found to be 0.25 for the left occipital area, 0.87 for the left motor area and 0.76 for the left frontal area. These figures are, of course, based on a small number of cases (11, 10 and 8 respectively), but it is possible that they represent a true trend. The greater the slow activity index prior to treatment, the greater this index after treatment.

8. Gibbs, F. A.: Cortical Frequency Spectra of Healthy Adults, J. Nerv. & Ment. Dis. **95**:417, 1942.

9. Lindquist,, E. F.: Statistical Analysis in Educational Research, Boston, Houghton, Mifflin Company, 1940.

Table 2 summarizes the data for the slow activity indexes for the 9 patients on whom records were obtained only after the course of treatment. These were arranged in increasing order with reference to the number of days after the termination of therapy. It is evident from these data, as well as from the data in table 1, that there is a differential susceptibility to metrazol of the processes underlying the development of slow activity. Records for patient 1 (table 2), for instance, who received six convulsive doses of metrazol, were taken one day after the last convulsion but exhibited a lower slow activity index than patient 2 (table 2), who received five convulsive injections and whose records were taken three days after termination of therapy. This differential effect is again seen when the values for patients 4 and 5 (table 2) are compared. Whether these differences were determined by the slow wave processes preceding treatment is essentially a matter of conjecture, but the data just cited suggest that this is a strong possibility. Because of this differential susceptibility, it is difficult to evaluate changes in the slow activity index with time except in individual cases. Mass data do not appear to be pertinent.

The measurements of alpha index, made prior to and after therapy, are also presented in table 1. From these data it is apparent that no systematic variation in alpha index appeared to follow metrazol therapy. Some patients exhibited striking increments in alpha activity, it is true, but others exhibited equally striking decrements. The average change (from the preshock to the first postshock record) was —0.6 for the left occipital area, + 3.4 for the left motor area and —0.1 for the left frontal area. Since these differences were so small, they were not treated statistically. They, obviously, are not significant, and one can conclude that no generalization from the data is permissible.

## COMMENT

These data indicate the following conclusions: There is an increase in the percentage of slow activity (less than 6 per second) in the electroencephalogram after metrazol-induced convulsions. This increase is significant in the motor and the frontal area but not in the occipital area. The increase is positively correlated with the amount of such slow activity prior to shock therapy (persons showing the highest preshock values tending to show the highest postshock values) in the motor and frontal areas. This differential susceptibility renders it difficult to plot "recovery" curves for the entire group of patients. There is no systematic alteration in alpha activity following metrazol-induced convulsions, although in individual cases pronounced increment or decrement may occur.

Our attempts to correlate increment in slow activity with clinical improvement have been negative, as have those of other workers (Polatin, Strauss and Altman [3]; Levy, Serota and Grinker [4]). Some investigators have reported that the appearance of the more extreme electroencephalographic abnormalities coincident to shock therapy (the abnormalities resembling the electroencephalogram of epileptic patients) is associated with the development of great mental confusion. In the light of the positive correlation between the slow activity index before and that after shock, one may infer, therefore, that persons with high slow activity indexes before shock therapy may be more susceptible to a confused mental state, and that this disturbance may appear with a smaller number of convulsions. Our own data are suggestive, but are insufficient to substantiate this hypothesis.

SUMMARY

Twenty depressed patients subjected to metrazol shock therapy were studied electroencephalographically. Eleven were studied before and after treatment; 9 after treatment only.

The following observations were made:

1. No significant group variation in the alpha index followed metrazol shock therapy, although there were striking individual changes.

2. There was significant variation in slow activity after such therapy.

3. This variation was made manifest as an increase in activity of less than 6 per second frequency in the motor and frontal areas.

4. There was evidence that the amount of slow activity following therapy was conditioned by the amount of such activity preceding therapy.

5. There was individual susceptibility to change in slow wave activity.

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# CHANGES IN THE ELECTROENCEPHALOGRAM FOLLOWING INSULIN SHOCK THERAPY

## A QUANTITATIVE STUDY

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In another communication [1] our associates and we have reported certain quantitative changes in the electroencephalogram following metrazol shock therapy. The subjects of that study were all patients with depressions. The significant changes in the electroencephalogram were found to be in the lower frequencies, those below 6 per second, these slow waves becoming more prominent after shock. No significant changes in alpha activity were noted, although in individual cases there were pronounced shifts upward and downward in the per cent time alpha.

The present report is concerned with a similar study of the electroencephalographic changes following insulin shock treatment of patients with schizophrenia.

### METHOD

Ten patients with schizophrenia, selected for treatment with insulin shock therapy, were utilized in this study. Nine of these patients received a similar course of thirty coma-producing treatments. Cortical potentials were recorded from the left occipital, the left motor and the left frontal area by means of three matched amplifiers and a Grass ink-writing oscillograph. Monopolar leads were used.

The records were analyzed as follows: Three samples, each 1 meter long (representing thirty-three and three-tenths seconds of recording), were selected at random from a continuous record of at least fifteen minutes' duration. The number of centimeters of each sample occupied by waves of a frequency of 6 per second or less was determined. Within the same samples the number of centimeters of alpha activity (8.5 to 12.5 per second frequency) was measured. These values were taken as the percentages of slow and alpha activity. Averages for the three samples, which are per cent time measurements, are referred to as the slow activity index and the alpha index respectively. It is possible for both slow and alpha activity to appear in the same strip of record, the latter being superimposed on the former.

In some instances, records from the frontal area were not suitable for analysis because of the occurrence of sweating or strong blinking during the recording.

### RESULTS

The results are summarized in the accompanying table. It is evident that the pretreatment values for the alpha index were higher than one would expect from the reports of other investigators (Lemere,[2] Davis [3] and Rubin [4]). After treatment some patients showed marked shifts in the alpha index. On the average

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1. Knott, J. R.; Gottlieb, J. S.; Leet, H. H., and Hadley, H. D., Jr.: Changes in the Electroencephalogram Following Metrazol Shock Therapy: A Quantitative Study, Arch. Neurol. & Psychiat., this issue, p. 529.

2. Lemere, F.: The Significance of Individual Differences in the Berger Rhythm, Brain **59**:366, 1936.

3. Davis, P. A.: Evaluation of the Electroencephalogram of Schizophrenic Patients, Am. J. Psychiat. **96**:851, 1940.

4. Rubin, M. H.: A Variability Study of the Normal and Schizophrenic Alpha Rhythm in Man, J. Psychol. **6**:325, 1938.

there was a slight increase in this index, the greatest increments being present in the motor and frontal areas. Were it not for patient 3, the group average would have shown a much more striking increase; because of the values for this single patient, the average difference for the alpha indexes before and after treatment is not statistically significant. When the values for the individual patients are viewed as 10 separate experiments, insulin shock therapy appears to produce an increase in alpha index, for 8 of the 10 patients showed such an increase, patients 3 and 9 being the exceptions. When the data for only the 8 patients are included in the averages, the mean increase in alpha index for the left occipital lobe was 10.3, for the left motor area 15 and for the left frontal area 19.9. This areal gradient of

*Per Cent Time Slow and Alpha Activities* in the Electroencephalograms of Schizophrenic Patients Before and After Insulin Shock Therapy*

| Patient No. | Relation of Record to Treatment | Area: Left Occipital S. I.† | Left Occipital A. I.† | Left Motor S. I. | Left Motor A. I. | Left Frontal S. I. | Left Frontal A. I. | Number of Comas Induced | Number of Days After Last Coma |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Before | 5.1 | 41.6 | 4.4 | 16.5 | 2.2 | 15.5 | | |
| | After | 0.9 | 50.1 | 4.2 | 50.4 | 2.1 | 25.7 | 30 | 3 |
| 2 | Before | 13.4 | 74.6 | 16.7 | 32.3 | .... | .... | | |
| | After | 1.7 | 75.1 | 1.9 | 34.7 | .... | .... | 30 | 10 |
| 3 | Before | 4.9 | 94.3 | 15.4 | 51.4 | 10.9 | 32.1 | | |
| | After | 20.4 | 20.8 | 23.3 | 6.9 | 12.3 | 4.4 | 30 | 2 |
| 4 | Before | 13.2 | 28.3 | 15.3 | 11.5 | 15.4 | 6.7 | | |
| | After | 18.0 | 41.8 | 29.7 | 9.1 | .... | .... | 30 | 5 |
| 5 | Before | 4.7 | 43.7 | 7.4 | 5.7 | .... | .... | | |
| | After | 13.9 | 59.9 | 18.6 | 19.8 | .... | .... | 18 | 3 |
| 6 | Before | 5.4 | 85.4 | 8.4 | 60.5 | 10.3 | 39.8 | | |
| | After | 7.8 | 92.5 | 18.9 | 85.9 | 18.4 | 76.1 | 30 | 12 |
| 7 | Before | 2.8 | 86.7 | 16.5 | 41.3 | 6.7 | 40.0 | | |
| | After | 7.8 | 96.4 | 25.1 | 61.2 | 16.0 | 67.0 | 30 | 8 |
| 8 | Before | 7.4 | 66.6 | 28.8 | 26.6 | 30.4 | 19.4 | | |
| | After | 13.7 | 91.9 | 22.6 | 63.4 | .... | .... | 30 | 4 |
| 9 | Before | 11.5 | 91.5 | 13.7 | 33.8 | 14.4 | 31.4 | | |
| | After | 26.2‡ | 52.5 | 23.7 | 36.0 | 20.0 | 20.3 | 30 | 1 |
| | After | 20.0 | 57.7 | 16.2 | 27.7 | 18.1 | 26.8 | 30 | 4 |
| 10 | Before | 25.4 | 58.6 | 23.3 | 58.9 | 19.0 | 54.9 | | |
| | After | 16.4 | 68.6 | 9.7 | 53.0 | 11.7 | 61.0 | 30 | 11 |
| Average | Before | 9.4 | 67.1 | 15.0 | 33.9 | 10.6 | 35.6 | | |
| | After | 12.1 | 65.7 | 17.0 | 41.2 | 13.1 | 43.5 | | |
| Difference..... | | +2.7 | —1.4 | +2.0 | +7.3 | +2.5 | +7.9 | | |

* By slow activity is meant frequencies of less than 6 per second, and by alpha activity, frequencies of 8.5 to 12.5 per second.

† S. I. indicates slow activity index and A. I., alpha index.

‡ Value not included in the average.

change is of interest in the light of the results with metrazol, which induced a similar areal gradient in the slow, rather than in the alpha, activity.

The slow activity index did not present striking deviations after insulin shock therapy. Such changes as did occur were equal in the three areas from which records were taken and were not statistically significant for any area.

## COMMENT

Perhaps the outstanding observation in this study was the increased rhythmicity of electric cortical discharge following insulin shock therapy. For 8 out of 10 patients this was made evident in the alpha index for the left occipital area, although for 1 of these patients the increase was so slight as to be attributed to chance. The remaining 2 patients (3 and 9) showed a decrease in the alpha index and an increase in the slow activity index (frequencies below 6 per second). Reinspection of the records for these 2 patients after insulin shock therapy revealed

more activity not only in the frequency bands below 6 per second but in the 6 to 8.5 per second bands, which were not quantitatively sampled. One may assume that this increase in the lower frequencies took place at the expense of 8.5 to 12.5 per second activity (alpha index). Thus, in cases in which an increase in alpha index was exhibited, the fundamental mechanism might be considered to involve a slowing of faster than alpha frequencies and their organization into rhythmic activity within a range of frequencies which by definition is called alpha. This situation is much the same as that obtained in sleep, in which the building up of activity in specific frequency bands involves a transposition downward of pre-existing faster activity (Knott, Gibbs and Henry.[5]).

SUMMARY

For 10 patients with schizophrenia electroencephalographic records were obtained before and after insulin shock therapy. Eight of the 10 patients exhibited an increase in the alpha index, which was more prominent in the frontal areas. Averages for the groups showed no striking deviations in slow activity. The increase in alpha activity may be due to slowing of preshock faster than alpha activity.

Iowa State Psychopathic Hospital.

5. Knott, J. R.; Gibbs, F. A., and Henry, C. E.: Fourier Transforms of the EEG During Sleep, J. Exper. Psychol. **31**:465, 1942.

# QUANTITATION OF MUSCULAR FUNCTION IN CASES OF POLIOMYELITIS AND OTHER MOTOR NERVE LESIONS

## ELECTRICAL EXCITABILITY TESTS AND ELECTROMYOGRAPHIC AND ERGOGRAPHIC STUDIES

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Accurate evaluation of muscular function is of clinical importance as an aid to diagnosis and prognosis in a number of neurologic conditions. It is essential for determination of the site and extent of injuries to peripheral nerves and is useful in establishment of the prognosis, particularly by early detection of signs of regeneration. In cases of poliomyelitis, tests of muscular function are of particular value when one is charting the degree of involvement and as a guide to muscle reeducation and evaluation of progress in response to therapy. The recent work of Kenny has brought fresh interest to the problem of behavior of muscle in the acute stage of this disease and has introduced new concepts of the symptoms and treatment. In order to assess the merits of her contribution, it is important to use objective and quantitative methods for measuring the performance of muscles.

At present the most generally used tests of muscular function in this disease are similar to the method described by Lovett.[1] In this method of examination the strength of individual muscles is graded according to their ability to overcome gravitational and manual resistances in prescribed positions. There is, inevitably, a large subjective element in such evaluations, with disagreement between observers. Although tests of this type are often of clinical value, they are not satisfactory as quantitative measurements, nor do they take into consideration the presence of "spasm." This symptom of poliomyelitis is assuming great importance since the advent of the Kenny theories. Clinical methods for detection of its presence are the means in most common use, but it is difficult to estimate the extent and severity of spasm without some accurate method, such as the recording of electrical potentials from the muscles.

Another method of examination frequently used is an assay of the electrical excitability of muscles to the make and break stimulus of a direct current, since the resultant contraction is qualitatively different in normal and in denervated

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1. Lovett, R. W.: Treatment of Infantile Paralysis, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1917, pp. 132-162.

muscles. A tetanizing current, such as the faradic or the 60 cycle alternating current, may also be used to test for the reaction of degeneration, as described by Erb.[2] A direct current with a slow rate of increase in potential further helps to indicate a change in irritability, since a normal muscle is able to accommodate such a slow increase in current with no resultant contraction, whereas a denervated muscle has lost this power of accommodation and responds with a slow, wavelike contraction. These methods have many limitations and at best give only an approximate idea of the excitability of the muscle, since small variations escape all but the most experienced and skilled observers and objective recordings are impossible.

These qualitative evidences of impaired electrical excitability may be quantitated by determination of the threshold of contraction for currents of measured intensity and duration. Chronaximetry is the familiar means employed for this purpose. According to Lapicque's[3] conception of a universal time factor, the duration threshold of response to a current of arbitrarily set intensity (twice the rheobase) is the important factor to be determined. It has been shown, however, that many factors, such as the type, position and size of the electrodes, greatly influence the results and that the concept of a universal time factor applies only under certain arbitrary or empiric conditions.[4] Furthermore, Rosenblueth and Dempsey[5] have shown that when the whole voltage-capacity curve is constructed, changes become apparent in the voltage parameter in degenerating nerves without alterations in the time parameter or the chronaxia. Since a change in either the voltage or the time parameter indicates a change in excitability, it seems that measurement of the strength-duration relationship over the entire curve is a superior method and avoids introduction of the arbitrary concept of chronaxia.

Since the clinical tests outlined here for evaluation of muscular function do not meet the requirements of objective measurement, a number of methods have been devised in this laboratory for quantitation of electrical excitability, work performance and electrical discharges of affected muscles in cases of poliomyelitis and other lesions of motor nerves.

## TECHNIC OF MEASUREMENT OF ELECTRICAL EXCITABILITY BY VOLTAGE-CAPACITY CURVES

The stimulating current used for this purpose is that of condenser discharges of measured capacity and voltage, varying from 0.0001 to 10 microfarads and 1 to 400 volts. The discharges are automatically controlled at a frequency of 12 per minute. The negative pole is used for the stimulating electrode, which usually consists of a small gage hypodermic needle inserted into the muscle at a recorded site. Sometimes a surface electrode is employed. This is either a thin disk of metal approximately 1 cm. in diameter, held in place by electrode paste and transparent adhesive tape, or a metal round tip electrode, held manually at a constant pressure, as measured by a spring balance incorporated in the handle. The positive pole is a large, dispersive electrode, placed in a neutral position on the patient.

The end point used is a threshold contraction as indicated by the just perceptible movement of the needle electrode or, in the case of the surface electrode, by the visible movement of the skin overlying the contracting muscle. From eight to sixteen determinations are made in both ascending and descending order. Voltage-capacity curves are plotted logarithmically,

2. Erb, W.: Zur Pathologie und pathologischen Anatomie peripherischen Paralysen. Deutsches Arch. f. klin. Med. **4**:535 (Oct.) 1868; **5**:42 (Nov.) 1868.

3. Lapicque, L.: Formule de l'excitabilité en fonction du temps, Compt. rend. Acad. d. sc. **179**:935-937, 1924.

4. Davis, H., and Forbes, A.: Chronaxie, Physiol. Rev. **16**:407-441 (July) 1936.

5. Rosenblueth, A., and Dempsey, E. W.: A Study of Wallerian Degeneration, Am. J. Physiol. **128**:19-30 (Dec.) 1939.

as suggested by Hill,[6] but do not fit his theoretic curves, as the shape is altered when stigmatic electrodes are used. Differences in cutaneous resistance are made negligible as compared with the total resistance obtained by 20,000 ohm shunt and series resistances being coupled in the circuit.

The results of a series of such tests are shown in figure 1. Voltage-capacity curves in these determinations were constructed for the extensor carpi radialis muscle in a study of the regenerative process in a patient whose injured radial nerve had been sutured. The improvement in excitability, as indicated by the results of these measurements, appeared before any clinical signs of regeneration were apparent. Other cases in which these methods were used have previously been described.[7]

Another method of objective evaluation of muscular function which is applicable to muscles activating the extremities is measurement of the amount of work of which the muscle is capable. For this purpose an ergograph has been designed in this laboratory which not only records each contraction of the muscle but measures the sum of the work done in any given period. This provides for an

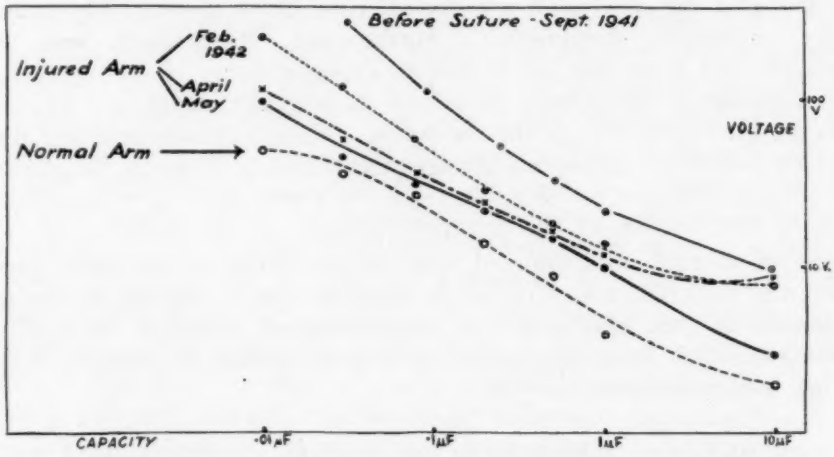


Fig. 1.—Voltage-capacity curves of the extensor carpi radialis muscle before and after suture of the radial nerve. Ordinate, $\log_{10}$ voltage; abscissa, $\log_{10}$ capacity.

objective, and much more accurate, measurement of the strength of the muscle than does the Lovett method of assessing the power exerted against manual and gravitational resistance.

## TECHNIC FOR MEASUREMENT OF WORK PERFORMANCE OF MUSCLES

The principle of the ergograph, a photograph of which is seen in figure 2, has a mechanical basis. That part of the limb which is activated by the affected muscle is attached to a weight by a string passed over a pulley, so that each contraction of the muscle lifts the weight. A pen writing on a revolving drum is actuated by the pulley through the same excursion as the weight. This drum is driven by a synchronous motor and has two speeds, 7 and 14 cm. per minute. The weight can be set to any value that is comparable to the amount of muscular force being tested.

6. Hill, A. V.: The Strength-Duration Relation for Electric Excitation of Medullated Nerve, Proc. Roy. Soc., London, s.B **119**:440-453 (March 2) 1936.

7. Watkins, A. L.: Electrical Aids in the Diagnosis and Prognosis of Nerve Injuries, Arch. Phys. Therapy **23**:76-83 (Feb.) 1942. Marble, H. C.; Hamlin, E., Jr., and Watkins, A. L.: Regeneration in the Ulnar, Median and Radial Nerves, Am. J. Surg. **55**:274-294 (Feb.) 1942.

An additional device attached to this apparatus enables the operator to quantitate the amount of work done per minute; this consists of a ticker tape on a revolving wheel, the tape being pulled through a ratchet each time the weight is lifted. In this manner, the total elevation of the weight, expressed in centimeters, can be measured by the length of the tape which passes through the ratchet. This length of tape, expressed in centimeters, multiplied by the weight lifted, expressed in grams, gives the amount of work done. An additional check on the amount of work done is given by the sum of the upward excursions of the pen on the drum. The tracing of the pen on the drum also gives a fatigue curve for the muscle under

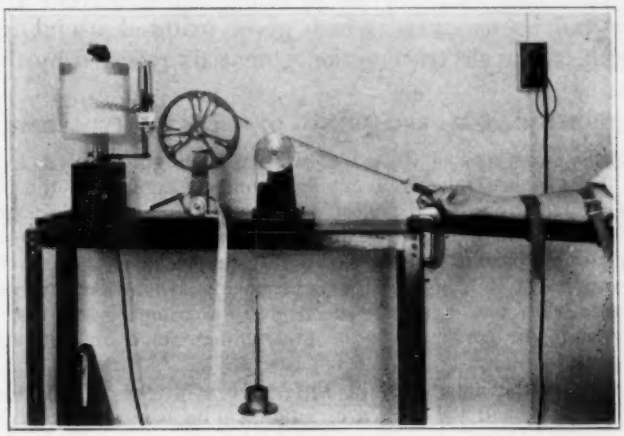

Fig. 2.—The ergograph used for recording and measuring the amount of work done by the contraction of a muscle.

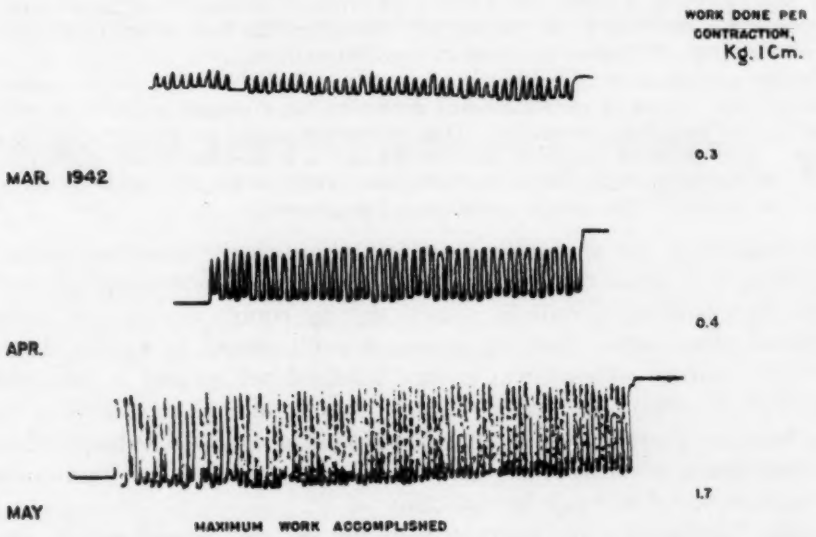


Fig. 3.—Ergograms recording the amount of work done by the arm in extension of the wrist at various stages of the regenerative process following suture of an injured radial nerve in the same case as that for which records appear in figure 1.

examination. Ergograms of muscular strength can be made at various stages of a disease process, or throughout the whole period of regeneration in the case of a recovering nerve lesion.

The results of a series of such ergographic determinations are shown in figure 3. These measurements were made in the same case of suture of an injured radial nerve as that shown in figure 1. Figure 3 shows clearly the steady increase

in the amount of work which the extensor carpi radialis muscle could accomplish in extension of the wrist as regeneration of the nerve progressed. Each contraction was recorded, the height of the excursion being proportional to the movement made; the average work done per contraction was calculated and entered in the right hand column. This method of measurement has been applied to the study of many types of injury to peripheral nerves and to studies of muscle in cases of poliomyelitis and infectious polyneuritis.

At the same time that an ergogram is being recorded from a working muscle, another property can be measured which gives material useful in both diagnosis and prognosis, that is, the electrical action potentials released by the muscle during contraction.

### TECHNIC FOR RECORDING OF ELECTROMYOGRAMS

Technics employing two types of electrodes were used in this study: 1. Surface electrodes made from solder disks, approximately 1 cm. in diameter, applied to the skin over the belly of the muscle with electrode paste and adhesive tape. A third electrode is placed on a neutral point to act as a ground. 2. Coaxial needle electrodes made by inserting an insulated core into a 24 gage hypodermic needle. These electrodes are placed in the muscle, and the outside of the needle is grounded. In some of the experiments synchronous recordings were made from the same muscle with both types of electrodes for comparison. Insulated copper wire from the electrodes leads the current into the preamplifier stage of a standard Grass electroencephalographic apparatus.

In the second stage of the apparatus the filters are arranged so that they may pass high frequency potential changes, and the degree of amplification is varied according to the amount of electrical discharge. Calibrations with a standard input are made with every recording, so that at any moment an exact assessment of the actual voltage elicited from the muscle can be made.

The final recording is made with a Grass ink-writing oscillograph on paper which is usually run through at a speed of 6 cm. per second; this speed has been found to give a satisfactory record of the range of frequencies found in muscular activity.

A further measurement of voltage is also made. The calibration already referred to gives a measure of the voltage of each individual deflection, but a summation of these voltages is also recorded by the use of an integrator. This instrument works on the principle of a condenser discharge: The incoming potentials are led through a condenser, which discharges each time it reaches its maximum load, and in discharging operates an electric signal on the same record on which the pattern of the muscle potentials is being traced.

An example of the application of this technic to the study of nerve regeneration is shown in figure 4. This figure illustrates the electrical action potentials from the extensor carpi radialis muscle during contraction in the subject whose strength-duration curves and ergograms are illustrated in figures 1 and 3. In figure 4 the amount of electrical energy released per second is computed on the right side of the chart. A steady increase is noticeable as regeneration progresses.

The electromyogram can be of considerable prognostic value, since traces of low voltage action potentials may be recorded on attempted contraction before any visible sign of movement can be detected.

Another application of electromyography is the recording of spontaneous electrical activity in resting muscles, such as is encountered with various types of nerve lesions. This is of especial interest in cases of poliomyelitis in view of Kenny's theory of "spasm" and has been intensively studied in this laboratory. The effects of the position of the limb and of passive and of voluntary movement on these discharges have also been studied and form the subject of another report.[8]

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8. Watkins, A. L.; Brazier, M. A. B., and Schwab, R. S.: Concepts of Muscle Dysfunction in Poliomyelitis, Based on Electromyographic Studies, J. A. M. A. **123**:188-192 (Sept. 25) 1943.

COMMENT

A threefold technic has been described for quantitative measurement of regeneration of injured peripheral nerves. This has been designed as a clinical laboratory procedure in our attempt to study the behavior of muscles in cases of poliomyelitis by more accurate methods than were heretofore available. It is not suggested that this battery of tests should be a part of the routine procedure or in any way a substitute for clinical observation. In many cases, however, such tests serve as a valuable adjunct to the usual methods of examination although for the trunk musculature, for example, it is obvious that this type of ergographic recording is not suitable. Nor is it always satisfactorily applicable to individual muscles serving joint movements which are activated by a complex of accessory muscles.

Study of muscular function in poliomyelitis was the primary object of these tests, but only a few new cases of the disease have been available to date (June 1943); consequently, injuries of peripheral nerves were the chief subject of investigation. We have had an opportunity to apply these methods of quantitation of regen-

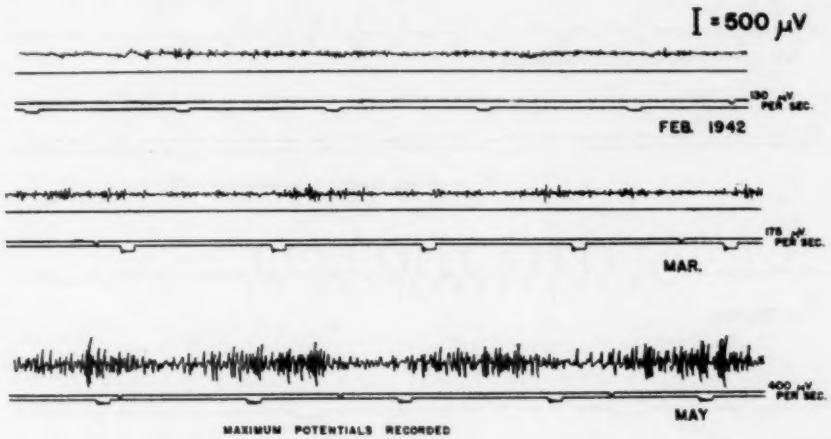


Fig. 4.—Action potentials from the extensor carpi radialis muscle during contraction at various stages of the regenerative process following suture of an injured radial nerve in the same case as that shown in figures 1 and 3. Under each electromyogram are two signal records: The lower one is the time marker, which records every second; the upper one, the integrator, which trips the signal at every condenser discharge. (Calibration: 1 signal per 700 microvolts.)

eration in 21 cases, including instances of lesions of the brachial plexus and the median, ulnar and radial nerves, and in 6 cases of infectious polyneuritis.

In the problem of diagnonsis these tests have proved of aid in determination of such questions as the degree and location of injury to a nerve and in the detection of hysterical components in cases of peripheral paralyses. A large number of the cases in which these technics have been applied have been those of service personnel suffering from war wounds in whom the degree of injury to the nerve was measurable by the tests for electrical excitability. The retention of good response to a tetanizing current, after the lapse of an adequate period to allow for the appearance of degenerative changes, is of course of great significance, as it indicates an incomplete lesion and, consequently, a relatively early return of function.

A difficult problem in war casualties is the localization of the level of nerve injury in cases of multiple wounds from gunshot or flying fragments. In these

instances tests for electrical excitability of the individual muscles reveal the distribution of involvement of the nerve, which might otherwise be obscured by limitation of movement due to lesions of bone, tendon or skin. As a case in which these objective tests were useful in detection of hysterical symptoms, we may cite that of a sailor who received an injury to his elbow resulting in apparently complete paralysis of the radial, median and ulnar nerves. Tests for electrical excitability showed that the injury was restricted to the radial nerve alone, with no involvement of the median and ulnar nerves at any time; even with evidence of progressive improvement in function of the radial nerve the patient retained his apparent paralysis.

These methods have also been used as prognostic leads. Since nerve regeneration after severe injury is necessarily a slow process, any test which will give early evidence of returning function is of value. As is known, the response to tetanic stimulation usually reappears only after return of voluntary motion, whereas improvement in electrical excitability as measured by voltage-capacity curves has been noted before clinical evidence of regeneration.

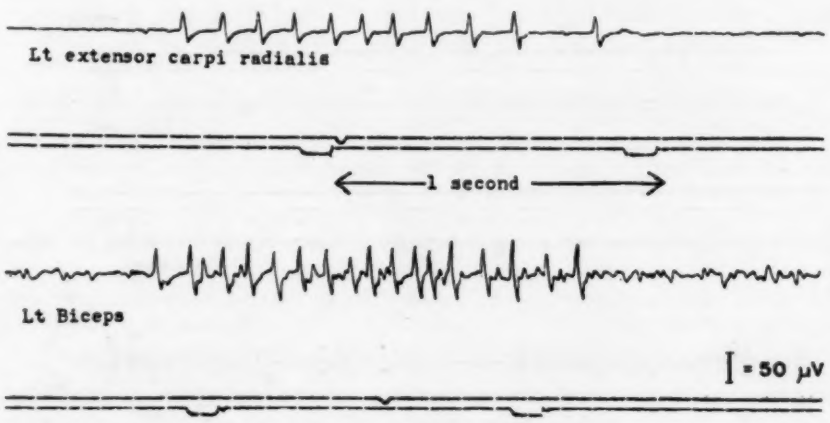


Fig. 5.—Spontaneous discharges in the relaxed muscles of the injured arm appearing twenty-two months after injury to the brachial plexus. The amplification is the same for both tracings.

Returning activity in the muscle can also be detected by the electromyogram during volitional efforts before any motion can be demonstrated either by observation or by the ergograph. A feature of the electromyogram, other than action potentials, which is of clinical significance is the appearance of spontaneous discharges in resting muscles. It may here be noted that ink-writing oscillographs are incapable of recording the fibrillation of denervation, since the speed of the pens is a limiting factor. This method, however, is satisfactory for the recording of motor unit activity. It had been planned to use a Dumont cathode ray oscilloscope and camera in these studies in order to obtain a faster speed of recording, but war conditions made it impossible to obtain the necessary short persistence, blue screen cathode ray tube.

In cases of lesions of peripheral nerves, before any clinical signs of regeneration could be detected, spontaneous discharges were recorded from the paralyzed muscles which were characteristic of motor unit activity; the appearance of these discharges was suggestive of nerve regeneration and, in fact, preceded other evidence of returning function (fig. 5).

The laboratory technics described in this paper not only have been of use in the study of injuries of peripheral nerves but have yielded material of interest in the

investigation of poliomyelitis and polyneuritis. In cases of the latter diseases the objective data are of aid in the evaluation of the newer types of therapeutic procedures and in elucidation of the more recent theories of their pathology.

Detailed reports dealing with the results of study in cases of poliomyelitis and polyneuritis have been made elsewhere.[9]

Miss Margaret Gray gave technical assistance in the recording of electromyograms and ergograms.

Massachusetts General Hospital.

9. Brazier, M. A. B.; Watkins, A. L., and Schwab, R. S.: Comparison of Muscle Dysfunction in Infectious Polyneuritis and Poliomyelitis, Based on Electromyographic Studies, New England J. Med., to be published.

# CEREBRAL ARTERIOVENOUS OXYGEN DIFFERENCE

## I. EFFECT OF AGE AND MENTAL DEFICIENCY

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The cerebral arteriovenous oxygen difference has been studied not only in normal subjects but in psychotic patients and in mentally defective persons. In the present investigation these studies were extended in order to determine the effect of age and mental deficiency on the cerebral arteriovenous oxygen difference. The subjects were normal babies less than 2 weeks of age and mentally deficient persons 6 to 55 years of age who belonged to the undifferentiated group, i. e., persons apparently normal except for their low intelligence.

### METHOD

Samples of blood were collected from the femoral or the brachial artery and the internal jugular vein. The method for the collection of the venous blood was that of Myerson, Halloran and Hirsch,[1] the needle being inserted in the internal jugular vein close to its point of exit from the cranial cavity through the jugular foramen. When the fontanel was patent, blood was drawn from the superior longitudinal sinus. Samples of blood were analyzed for oxygen by the method of Van Slyke and Neill.[2]

### RESULTS

The following tabulation reveals arteriovenous oxygen differences for normal children under 2 weeks of age. The average of the differences between the oxygen content of the arterial and that of the fontanel blood for 11 babies was 8.6 volumes

| Cerebral Arteriovenous Oxygen Differences, Volumes per Cent | |
|---|---|
| 7.4 | 8.3 |
| 8.6 | 6.7 |
| 8.3 | 6.0 |
| 10.8 | 9.8 |
| 10.5 | 8.6 |
| 9.5 | |
| | Average 8.6 |

per cent. In 1 observation the difference in the oxygen content of the arterial blood and that of the internal jugular venous blood was 8.2 volumes per cent. The accompanying table discloses the cerebral arteriovenous oxygen differences for undifferentiated mentally defective persons. These subjects were divided into two series: the first with intelligence quotients of from 8 to 49, and the second with intelligence quotients of from 50 to 88. Each series was further divided into

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1. Myerson, A.; Halloran, R. D., and Hirsch, H. L.: Technic for Obtaining Blood from the Internal Jugular Vein and the Internal Carotid Artery, Arch. Neurol. & Psychiat. **17**:807-808 (June) 1927.

2. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in the Blood and Other Solutions by Vacuum Extraction and Manometric Measurements, J. Biol. Chem. **61**:523-573, 1924.

five age groups: from 6 to 9 years, from 10 to 14 years, from 15 to 19 years, from 20 to 29 years and from 30 to 55 years. The average cerebral arteriovenous oxygen differences for the age groups of each series, as well as for the two series combined, 130 patients in all, are presented.

## COMMENT

The average cerebral arteriovenous oxygen differences for the corresponding age groups of the two series of patients with intelligence quotients of from 8 to 49 and from 50 to 88 respectively were not significantly unlike each other. For that reason results for all subjects in each age group were averaged. These averages revealed a progressive increase in the average cerebral arteriovenous oxygen differences in the first four age groups. From a statistical analysis it may be concluded that these results do show a progressive biologic change, which reaches a maximum at the age of 20 to 29 years and then remains unaltered until the age of 55 years. This analysis, made with the aid of Fisher's [3] $t$ criterion, proves that the differences between these averages are significant, with one exception: the difference between the averages for the first two groups. Since this is the only value that is not significant, we feel it likely that with a greater number of subjects this difference would also become significant.

*Average Cerebral Arteriovenous Oxygen Differences for Undifferentiated Mentally Defective Subjects at Various Ages*

| | Volumes per Cent | | | | |
|---|---|---|---|---|---|
| | 6-9 Yr. | 10-14 Yr. | 15-19 Yr. | 20-29 Yr. | 30-55 Yr. |
| Undifferentiated (I. Q. 8-49) | 4.5 (17)* | 5.4 (13) | 5.7 (14) | 6.6 (12) | 6.7 (19) |
| Undifferentiated (I. Q. 50-88) | 4.9 (13) | 5.0 (20) | 6.3 (8) | 6.6 (9) | 6.2 (5) |
| Total | 4.7 (30) | 5.1 (33) | 5.9 (22) | 6.6 (21) | 6.6 (24) |

* Numbers in parentheses indicate the number of observations from which the average values were obtained.

In order to evaluate the significance of these averages, it is necessary to compare them with the averages for persons with normal intelligence. From a large series of observations on normal subjects above 20 years of age, an average cerebral arteriovenous oxygen difference of 6.7 volumes per cent has been obtained. This value is derived from the values of 6.4,[4] 6.7 [5] and 6.9 volumes per cent [6] observed for three groups of 21, 50 and 23 normal persons respectively. The undifferentiated mentally defective person over 20 years of age (table), therefore, showed a normal cerebral arteriovenous oxygen difference.

The chief importance of the cerebral arteriovenous oxygen difference lies in the fact that it is one of the two factors necessary for measurement of the cerebral metabolic rate: The cerebral arteriovenous oxygen difference per unit of blood multiplied by the cerebral blood flow yields the cerebral metabolic rate. In our subjects there was no indication of any change in cerebral blood flow because there was no apparent pathologic alteration in the pulmonary, cardiac or circu-

3. Fisher, R. A.: Statistical Methods for Research Workers, London, Oliver & Boyd, Ltd., 1928.

4. Gibbs, E. L.; Lennox, W. G., and Gibbs, F. A.: Variations in the Carbon Dioxide Content of the Blood in Epilepsy, Arch. Neurol. & Psychiat. **43**:223-239 (Feb.) 1940.

5. Gibbs, E. L.; Lennox, W. G.; Nims, L. F., and Gibbs, F. A.: Arterial and Cerebral Venous Blood: Arterial-Venous Differences in Man, J. Biol. Chem. **144**:325-332, 1942.

6. Wortis, J.; Bowman, K. M., and Goldfarb, W.: Human Brain Metabolism: Normal Values and Values in Certain Clinical States, Am. J. Psychiat. **97**:552-565, 1940.

latory system. It may, therefore, be assumed that the cerebral blood flow of these subjects was normal. With a normal cerebral blood flow and normal oxygen differences it may be concluded that at least for undifferentiated mentally defective persons between the ages of 20 and 55 years there was no alteration in the cerebral metabolic rate. The mental deficiency of these subjects cannot be ascribed to depressed utilization of oxygen. The formation of energy was unchanged; its utilization, however, was disturbed.

It has not been possible to compare the cerebral arteriovenous oxygen differences for the undifferentiated mentally defective subjects below 20 years of age because there are few, if any, values in the literature for younger normal subjects. If, however, the results for the subjects above 20 years of age may be taken as a criterion, the possibility arises that the cerebral arteriovenous oxygen differences for the undifferentiated mentally defective persons of the various age groups studied were the same as those of persons with higher intelligence quotients. In that case an examination of the effects of age on the cerebral arteriovenous oxygen differences of undifferentiated mentally defective persons yields information not only on this group of subjects but on normal subjects. This suggests that the increasing cerebral arteriovenous oxygen differences for the first four age groups may be the same as those for normal subjects. To summarize, not only were the average cerebral arteriovenous oxygen differences for the undifferentiated mentally defective subjects between the ages of 6 and 55 years the same for the corresponding age groups, irrespective of the intelligence quotient, but they were probably the same as those for normal persons with intelligence quotients above 80.

The increase in the cerebral arteriovenous oxygen differences for the four age groups from 6 to 29 years may indicate an increase in the cerebral metabolic rate. There is evidence from many sources that there is an acceleration of cerebral metabolism as growth proceeds. Our observations on excised cerebral tissues from newborn rats disclosed a metabolic rate at birth lower than that of the adult.[7] Tyler and Harreveld[8] found three levels of metabolism during the life span of the rat: a low rate in the first week of life; then a period of rapid rise to a maximum from the fourth to the seventh week, and, finally, a slight and slow decrease to the twentieth week. These results extend to the observations on metabolic rate previously made on puppies,[9] which revealed an acceleration of cerebral metabolism from birth to 5 to 7 weeks of age and then a slight, but steady, decline thereafter. The chief difference between cerebral metabolism in the human subject and that in the lower mammals is not in the kind of changes but, rather, in the length of time required to produce them. In the human subject the various alterations in cerebral metabolic rate probably occur over much longer periods, and the maximum value is not attained until 20 years of age. The human electroencephalogram assumes full adult features at approximately the same time.[10]

The only exceptions to the low cerebral arteriovenous oxygen difference in early life are the observations made on normal infants less than 2 weeks of age. Observations on 11 newborn infants yielded an average cerebral arteriovenous oxygen difference of 8.6 volumes per cent. This value is significantly higher than that for the normal adult, which averages 6.7 volumes per cent. The greater

7. Himwich, H. E.; Baker, Z., and Fazekas, J. F.: The Respiratory Metabolism of Infant Brain, Am. J. Physiol. **125**:601-606, 1939.

8. Tyler, D. B., and van Harreveld, A.: The Respiration of the Developing Brain, Am. J. Physiol. **136**:600-603, 1942.

9. Himwich, H. E., and Fazekas, J. F.: Comparative Studies of the Metabolism of the Brain of Infant and Adult Dogs, Am. J. Physiol. **132**:454-459, 1941.

10. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Lew A. Cummings Company, 1941.

cerebral arteriovenous oxygen difference in the newborn indicates either (1) a higher rate of cerebral metabolism in the infant or (2) a slower cerebral blood flow so that more oxygen is taken from each unit of blood circulating through the brain. According to MacArthur and Doisy,[11] growth of the human brain is most rapid at the time of birth. If this growth requires a large complement of energy, it is possible that the high cerebral arteriovenous oxygen difference is caused by a high rate of cerebral metabolism. On the other hand, direct observations on cerebral metabolism of all mammals studied have revealed that the cerebral metabolic rate is lower at birth than at any other period of extrauterine life. Similar observations [12] on excised cerebral tissues have been made on human fetuses 5 and 6 months of age and on adults. Comparison of the cerebral metabolic rate in the fetus and that in the adult indicates that the fetal rate is one-third that of the adult. If the cerebral metabolism is low at birth, one is left with the second possibility to explain the high cerebral arteriovenous oxygen difference, namely, a slow rate of blood flow through the brain. It has been observed that the rate of cerebral blood flow varies directly with the systemic blood pressure.[13] The blood pressure of a 24 hour old, full term infant averages 80 mm. of mercury systolic and 46 mm. diastolic [14] and increases slightly during the first ten days of life. These low levels of blood pressure apply to the infants used in the present observations, since they were less than 2 weeks old. It is probable therefore that their large arteriovenous oxygen differences can be ascribed to a slow cerebral blood flow, and not to a high cerebral metabolic rate. At present, however, a final decision between these two possibilities cannot be made.

There are two series of observations on cerebral arteriovenous oxygen differences at the other extreme of life, the senium. The average for one series, consisting of 15 patients with cerebral arteriosclerosis, 59 to 97 years of age, was 6.7 volumes per cent,[6] and that for the other series, of 23 patients, 60 to 87 years of age, was 6.8 volumes per cent,[15] values indistinguishable from those for younger normal adults. But if the cerebral blood flow diminishes in old age, then cerebral metabolism also decreases despite a constant cerebral arteriovenous oxygen difference. There are data indicating that chronic degenerative changes in the brain may be accompanied by adaptive reductions in cerebral blood flow. Rosenbaum, Roseman, Aring and Ferris [16] observed decreases in intracranial blood flow in patients with cerebral arteriosclerosis.[17] The graph (figure) presented includes all the data discussed in this communication on the relationship of cerebral arteriovenous oxygen differences to age. Increases are observed in the four stages from 6 to 9 years, from 10 to 14 years, from 15 to 19 years and from 20 to 29 years. Then the value remains the same until extreme old age. No data are available on

11. MacArthur, C. G., and Doisy, E. A.: Quantitative Chemical Changes in the Human Brain During Growth, J. Comp. Neurol. **30**:445-486, 1918-1919.

12. Racker, E.: Observations on the Metabolism of Human Fetal Brain in Vitro, Federation Proc. **1**:69, 1942.

13. Forbes, H. S.: Physiologic Regulation of the Cerebral Circulation, Arch. Neurol. & Psychiat. **43**:804-814 (April) 1940.

14. Woodbury, R. A.; Robinow, M., and Hamilton, W. F.: Blood Pressure Studies on Infants, Am. J. Physiol. **122**:472-479, 1938.

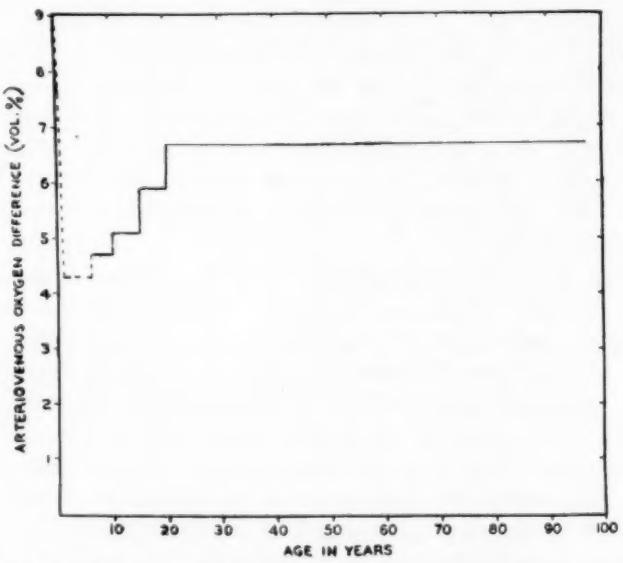
15. Cameron, D. E.; Himwich, H. E.; Rosen, S. R., and Fazekas, J. F.: Oxygen Consumption in the Psychoses of the Senium, Am. J. Psychiat. **97**:566-572, 1940.

16. Rosenbaum, M.; Roseman, E.; Aring, C. D., and Ferris, E. B., Jr.: Intracranial Blood Flow in Dementia Paralytica, Cerebral Atrophy and Schizophrenia, Arch. Neurol. & Psychiat. **47**:793-799 (May) 1942.

17. Aring, C. D.: Personal communication to the authors.

infants from 1 to 5 years of age. If, however, the oxygen intake during this five year period proceeds in the same sequence in which it does during the entire period of growth, then we are tempted to conclude that it would be even lower for children from 1 to 5 years of age than it is for those from 6 to 9 years of age. For the newborn baby the cerebral arteriovenous oxygen difference is high.

A suggested graph for cerebral metabolic rates might be similar to that for cerebral arteriovenous oxygen differences except for the two extremes of life. The steady rise in cerebral metabolic rate from 6 to 9 years, 10 to 14 years, 15 to 19 years and 20 to 55 years would still be present. In the newborn and in the aged, however, it is possible that slow cerebral blood flow increases the cerebral arteriovenous oxygen difference and that the cerebral metabolic rate is relatively low at these times of life. Cerebral metabolism may be lowest in the newborn and, after attaining its highest value in adults from 20 to 55 years of age, may decrease somewhat during the senium.




Relationship of cerebral arteriovenous oxygen difference to age.

Alterations in cerebral metabolism may be caused by changes in one or more of the three essential factors of cerebral metabolism: oxygen, blood sugar and respiratory enzymes. Since our subjects revealed neither anoxia nor hypoglycemia, the variations in cerebral metabolism must have resulted from differences in the concentrations of respiratory enzymes. There is evidence that the heightened cerebral metabolism may be ascribed to an increasing concentration of cerebral respiratory enzymes during growth.[18]

## SUMMARY

The cerebral arteriovenous oxygen differences for undifferentiated mentally defective persons reveal a significant and progressive increase during growth. The values are 4.7 volumes per cent for the ages of 6 to 9 years, 5.1 volumes per cent for the ages of 10 to 14 years, 5.9 volumes per cent for the ages of 15 to 19 years and

18. Himwich, H. E.; Bernstein, A. O.; Fazekas, J. F.; Herrlich, H. C., and Rich, E.: Metabolic Effects of Potassium, Temperature, Methylene Blue, and Paraphenylenediamine on Infant and Adult Brain, Am. J. Physiol. **137**:327-330, 1942.

6.6 volumes per cent for the ages of 20 to 55 years. For the newborn the cerebral arteriovenous oxygen difference averages 8.6 volumes per cent.

The cerebral arteriovenous oxygen differences for undifferentiated mentally defective persons are the same for the corresponding age groups whether the intelligence quotients of the subjects are from 8 to 49 or 50 to 88.

The average cerebral arteriovenous oxygen difference for 45 undifferentiated mentally defective persons from 20 to 55 years of age is 6.6 volumes per cent, a value not significantly different from that for persons with greater intelligence. Since there is no evidence to indicate that the cerebral blood flow in these subjects was changed from the normal, it is concluded that the cerebral metabolic rate of undifferentiated mentally defective persons from 20 to 55 years of age is not changed from the normal and that their mental deficiency is not caused by an impaired cerebral metabolic exchange.

It is suggested that the cerebral arteriovenous oxygen differences for the undifferentiated mentally defective persons of the five age groups from 6 to 55 years are similar to those for persons with higher intelligence quotients.

The high average cerebral arteriovenous oxygen difference for infants less than 2 weeks old may be due to a slow cerebral blood flow and may occur despite a low cerebral metabolic rate.

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# RETICULUM CELL SARCOMA OF THE BRAIN

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In former times it was customary to designate any rapidly growing, fleshy, highly cellular tumor of the brain by the generic term "sarcoma," and in all early statistical analyses sarcomas were the largest and most important group of cerebral tumors. With the development of improved methods for the staining of different histologic structures many of these malignant growths were reclassified as gliomas, and the sarcomas, i. e., tumors derived from embryonic connective tissue, were found to be exceedingly rare.

It was Bailey [1] who, in 1929, reawakened interest in sarcomas of the brain by reporting several types of malignant tumors arising from the leptomeninges. Some of these tumors were obviously derived from fibroblasts and others from the melanophore cells. Many, however, were so anaplastic that the "type cell" could not be identified, and the growths were classified by him as perithelioma, perithelial sarcoma and alveolar or round cell sarcoma, depending on whether tumor cells invaded the perivascular space or formed a solid mass in the substance of the brain.

The more recent contributions to the subject of sarcomas of the brain have been directed toward the identification of that tumor which Bailey (1929) termed perithelial sarcoma. Yuile,[2] in 1938, reported a tumor of the brain which he concluded to be a reticulum cell sarcoma, or microglioblastoma, and in the same year Ferens [3] described a similar case of "reticuloendothelioma." In 1940 Hsü [4] presented another case of perithelial sarcoma in which complete autopsy was performed, as well as a case without complete autopsy of a tumor which he designated as alveolar sarcoma. Benedek and Juba,[5] in 1941, studied a case of a tumor which they concluded was of microglial origin, a "microglioma." Fried,[6] 1926, and Mage and Scherer,[7] 1937, recorded similar cases, but complete autopsies were not performed; thus cerebral metastasis could not be absolutely excluded.

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From the Mallory Institute of Pathology, Boston City Hospital (Dr. Kinney) and the Neurological Unit, Boston City Hospital, and Department of Neurology, Harvard Medical School (Dr. Adams).

1. Bailey, P.: Intracranial Sarcomatous Tumors of Leptomeningeal Origin, Arch. Surg. **18**:1359-1402 (April) 1929.

2. Yuile, C. L.: Case of Primary Reticulum Cell Sarcoma of the Brain: Relation of Microglia Cells to Histiocytes, Arch. Path. **26**:1036-1044 (Nov.) 1938.

3. Ferens, E.: Case of Primary Reticulo-Endothelioma of Central Nervous System, Neurol. polska **21**:387-402, 1938.

4. Hsü, Y. K.: Primary Intracranial Sarcomas, Arch. Neurol. & Psychiat. **43**:901-924 (May) 1940.

5. Benedek, L., and Juba, A.: Microglioma, Gyógyászat **81**:223-226, 1941; Ueber das Mikrogliom, Deutsche Ztschr. f. Nervenh. **152**:159-169, 1941.

6. Fried, B. M.: Sarcomatosis of the Brain, Arch. Neurol. & Psychiat. **15**:205-217 (Feb.) 1926.

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Tumors of this type, primary in the brain and variously classified as perithelial sarcoma, reticulum cell sarcoma and microglioma, constitute the material of this paper. The clinical and pathologic material in 2 additional cases is reported and compared with that in similar cases recorded in the medical literature. The possible relationship of this tumor to the reticuloendothelial system, particularly to the element known as the microglia, is discussed.

## EMBRYOLOGIC CONSIDERATIONS

Although there would seem to be an abundance of tissue in the brain from which malignant connective tissue tumors could develop, it should be remembered that much of the interstitial tissue is neuroglial and therefore of ectodermal, rather than of mesodermal, origin. Only the leptomeninges and their perivascular projections, which Bailey termed the "perithelium," contain connective tissue elements. It is generally believed that the microglial cells, which are now generally conceded to be of mesodermal origin, do not undergo neoplastic change.

The leptomeninges appear to develop from mesenchymal tissue, but it is still unsettled whether they arise from ectoderm or from mesoderm. Histologically, the pia and the arachnoid are composed of fibroblasts and collagen fibrils, histiocytes and melanophore cells and are lined by specialized fibroblasts, known also as arachnoid cells. Each of these various cell types possesses characteristic morphologic features and theoretically could give rise to tumors distinguished by these same features. A tumor arising from the fibroblast would, accordingly, be a fibroblastoma (fibroma or fibrosarcoma); one arising from the arachnoid cells would be a meningioma, while a tumor arising from the melanophore cells would be a melanotic carcinoma. The histiocyte, or its immediate progenitor, would give origin to the reticulum cell sarcoma.

The perithelium of cerebral vessels consists of intracerebral extensions of the pia-arachnoid and could theoretically undergo the same neoplastic transformations as the aforementioned cells.

The microglia cells, according to the investigations of del Río Hortega, are derived during early fetal life from the pia and invade the brain at certain fixed points, the most important of which are the cerebral peduncles and the tela choroidea of the lateral, third and fourth ventricles. The original cell in the pia from which the microglioblast arises is still undetermined, although the most likely possibility is the histiocyte or the more primitive reticular cell. This is suggested by the work of Jíminez de Asua [8] and Dunning and Furth,[9] which shows that microglial cells have the same staining potentialities and are activated by the same stimuli as histiocytes in any other organ of the body, such as Kupffer cells in the liver and reticulum cells in the spleen and lymph nodes. Microglioblasts migrate throughout the central nervous system. In accordance with what has been learned from the study of tumors developing from the reticuloendothelial system in other organs of the body, the microglioblastoma should closely resemble the reticulum cell sarcoma.

In summary, it seems theoretically possible that three types of malignant mesoblastic tumors may develop within the brain or its coverings: the fibrosarcoma, the malignant meningioma and the reticulum cell sarcoma.

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8. Jíminez de Asua, F.: Die Mikroglia und das reticulo-endotheliale System, Ztschr. f. d. ges. Neurol. u. Psychiat. **109**:354-379, 1927.

9. Dunning, H. S., and Furth, J.: Studies on the Relation Between Microglia, Histocytes and Monocytes, Am. J. Path. **11**:895-913, 1935.

## REPORT OF CASES

CASE 1.—*History.*—The patient, a Portuguese painter aged 66, was unable to give an accurate account of his illness, but from various sources it was learned that he had been suffering from headaches and had been excessively irritable during the previous two months. On one occasion, two weeks before admission to the Boston City Hospital, he suddenly became faint and dizzy. On the night before admission he was arrested by the police, who found him staggering about in the street. It was noticed that he was not drunk but was confused and irrational.

*Examination.*—At the time of admission the temperature was 99 F., the respiratory rate 22, the pulse rate 88 and the blood pressure 134 systolic and 76 diastolic. The patient was well developed and fairly well nourished. He was confused and disoriented in all spheres. Even simple questions were answered by short, meaningless words or phrases. Cooperation during the examination was poor. Tests for aphasia showed that he was unable to carry out complicated commands. There was a definite tendency to perseverate. He could read individual letters and simple words but was unable to comprehend their meaning. He had difficulty in

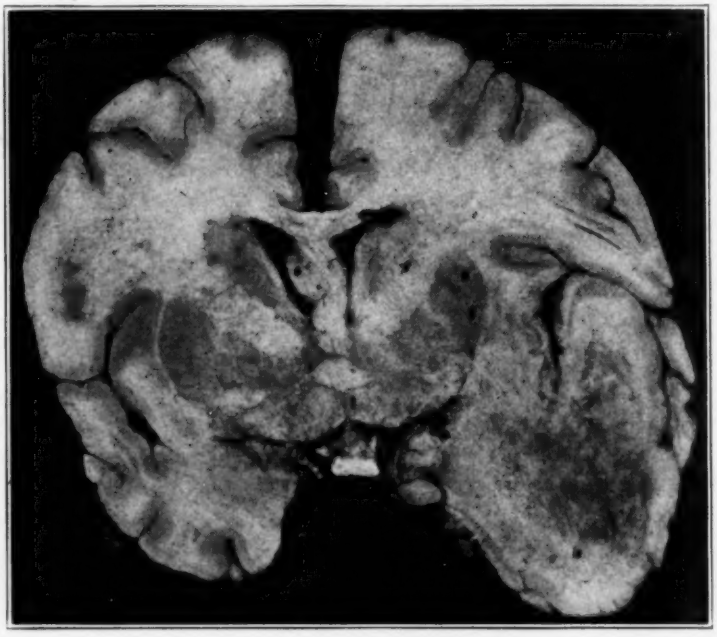

Fig. 1 (case 1).—Reticulum cell sarcoma of the left temporal lobe. × 750.

naming common objects and was unable to write. The optic fundi, pupillary reactions, extraocular movements and functions of the rest of the cranial nerves were within normal limits. There was no incoordination in movements of the arms or legs. Painful stimuli were felt equally well on the two sides of the body, but the confused sensorium prevented more accurate sensory tests. Tendon reflexes were active and equal on the two sides, and plantar responses were bilaterally flexor in type.

*Laboratory Data.*—The hemoglobin concentration was 76 per cent (Sahli); the red blood cell count, 3,950,000, and the white blood cell count, 7,650. The Hinton reaction of the blood was negative. The nonprotein nitrogen content of the blood was 30 mg. per hundred cubic centimeters. Urinalysis revealed nothing abnormal except for the presence of a small amount of albumin. Studies of the cerebrospinal fluid revealed a pressure of 100 mm. of water; 31 lymphocytes per cubic millimeter, and 166 mg. of protein, 60 mg. of sugar and 708 mg. of chlorides per hundred cubic centimeters. The colloidal gold curve was 0010000000, and the Wassermann reaction was negative.

A pneumoencephalogram showed no filling of the left lateral ventricle and slight downward displacement of the right lateral ventricle. No air was present in the left subarachnoid space. These observations were thought to be consistent with the presence of a space-occupying lesion in the left frontoparietal region. An electroencephalogram showed a focus of slow waves in the left posterior frontal area.

*Course of Illness.*—While in the ward the patient gradually became stuporous. On the twelfth day in the hospital examination revealed the following additional neurologic signs: bilateral sucking reflexes; right hemiparesis, involving the face, arm and leg; slightly increased tendon reflexes on the right side; diminished abdominal reflexes on the right side; a positive Chaddock reflex on the right side and a questionable one on the left, and urinary incontinence.

A ventriculogram was made on the eighteenth day of hospitalization. Both ventricles filled with air and were noted to be pushed to the right. The anterior horn and the body of the left lateral ventricle appeared to be compressed.

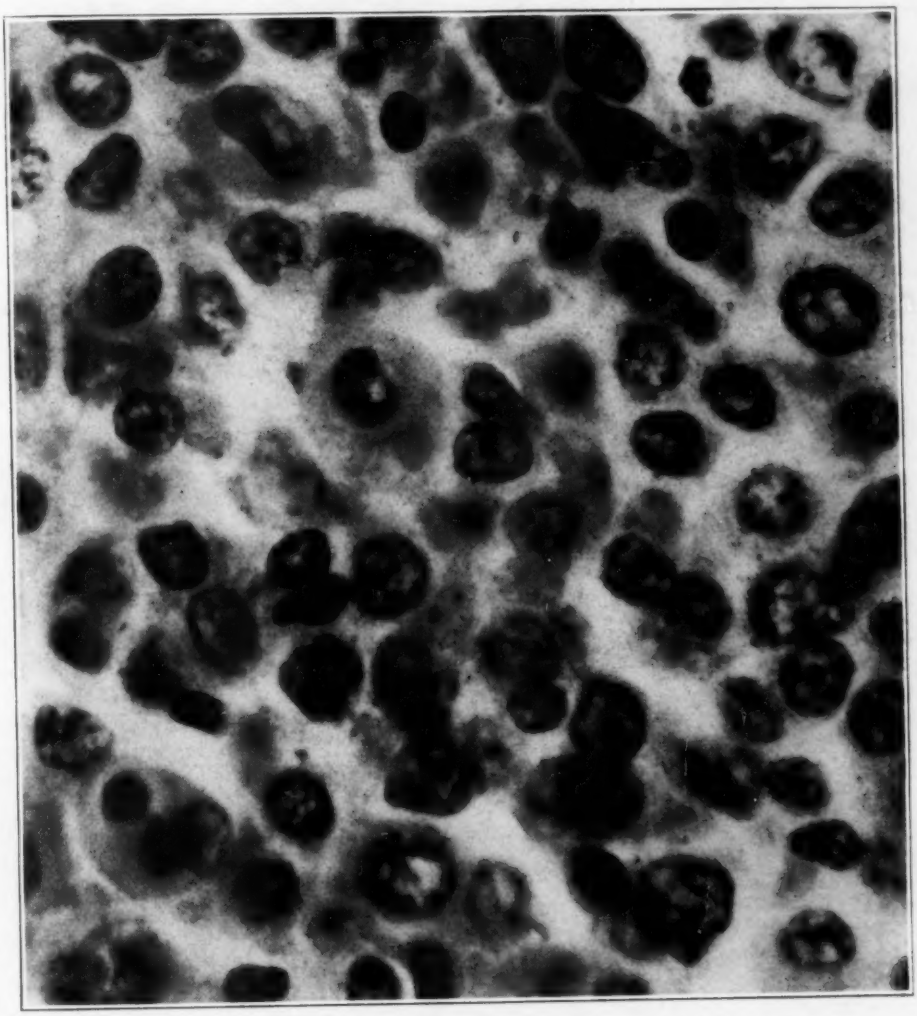

Fig. 2 (case 1).—Tumor showing ameboid activity and phagocytosis. Phloxine-methylene blue stain. × 750.

On the nineteenth day in the hospital the patient's temperature rose to 102.8 F., the pulse rate to 160, the respiratory rate to 42 and the blood pressure to 150 systolic and 90 diastolic. He perspired freely and appeared very sick. The spinal fluid pressure at this time was 250 mm. of water. There was evidence of pulmonary edema. The patient's condition remained unchanged for twelve hours, and in spite of supportive treatment, he died during the early morning of the twentieth day in the hospital.

*Postmortem Examination.*—External examination of the body revealed nothing of note. The brain weighed 1,540 Gm. The cerebral convolutions were conspicuously flattened and the sulci narrowed. The subarachnoid spaces over the cerebral hemispheres contained little

cerebrospinal fluid. The left temporal lobe was significantly larger than the right, and the convolutions over this lobe were abnormally broad. The left hippocampal gyrus had herniated into the notch of the tentorium, displacing the midbrain to the right. Sections in the coronal plane disclosed a tumor mass in the left temporal lobe which had replaced the central and convolutional white matter (fig. 1). The tumor had extended medially into the lower portion of the insula, the claustrum, the external capsule, the tail of the caudate nucleus and the amygdaloid nucleus. The lenticular nucleus, the internal capsule, the thalamus and the head of the caudate nucleus were spared. The cerebral cortex was not invaded, and the leptomeninges were not grossly involved. The tumor measured 6 by 5 by 4 cm. and was

Fig. 3 (case 1).—Reticulum surrounding individual tumor cells. Foot's reticulum stain. × 750.

homogeneous, pink-gray and soft in consistence. There were no areas of cavitation, necrosis or hemorrhage. The temporal horn of the left lateral ventricle was obliterated, and both lateral ventricles and the third ventricle were displaced to the right.

Tissue from the tumor was fixed in a Zenker's fluid and a 10 per cent concentration of solution of formaldehyde U. S. P. and stained with phloxine–methylene blue (methylthionine chloride), phosphotungstic acid hematoxylin, Laidlaw's reticulum stain and Foot's modification of the Hortega stain for reticulum.

Microscopic examination showed that the tumor was composed of rather large cells containing a moderate amount of cytoplasm and single round to oval nuclei (fig. 2). There were no tumor giant cells, although an occasional binucleated cell was present. The cells were uni-

form in size and shape and usually measured from 12 to 14 microns in diameter. The nuclei were generally round or oval and were occasionally indented. The nuclear chromatin was arranged in a delicate network. The cell cytoplasm was clear and rather scanty. Nucleoli were not prominent. Mitoses were common. Many of the tumor cells showed pseudopodic projections, suggesting ameboid activity. Phagocytosis was a prominent feature. The cells were grouped closely together and were most abundant around blood vessels. There was considerable reticulum throughout the tumor, which surrounded both individual cells and groups of cells. A phosphotungstic acid hematoxylin stain failed to show fibrils arising from the tumor cells. In sections prepared by the Foot-Hortega stain, an abundant coarse reticulum which surrounded both individual cells and groups of cells was demonstrated, but here, too, there was no evidence that these fibers originated from the tumor cells (fig. 3).

The right and left lungs each weighed 660 Gm. and appeared grossly similar. They were dark red-blue, boggy and subcreptitant. The bronchial mucosa was dull and red-gray, and the bronchi contained large quantities of yellow to green mucoid material. Microscopic sections showed bronchopneumonia and moderate pulmonary congestion and edema. There were several small, slightly depressed scars over the surface of the kidney, which on microscopic examination were seen to be areas of healed focal pyelonephritis.

*Anatomic Diagnosis.*—The diagnosis was (1) primary reticulum cell sarcoma of the brain, involving the left temporal lobe, with a tentorial herniation on the left side; (2) pulmonary congestion and edema, and (3) healed focal pyelonephritis, of mimimal degree.

At the time of entry to the hospital the patient was demented and aphasic. The insidious onset, the gradual progression of symptoms and the increasingly severe headaches were all indicative of tumor of the left cerebral hemisphere. In view of the short course of the illness, glioblastoma multiforme or metastatic carcinoma was considered to be the most likely possibility. Operation was delayed because of the patient's poor physical condition. Autopsy revealed that the tumor was confined to the left temporal lobe.

Case 2.—*History.*—A Negro aged 72 entered the Boston City Hospital complaining of headache, weakness and excessive fatigability of approximately three months' duration. At the onset of his illness it was observed that he was unusually drowsy during the daytime. When walking he appeared to stagger toward the left. A few weeks later his family noted that he talked incoherently and was somewhat confused. The headaches, which had developed recently, were of increasing severity. A few days before entrance to the hospital he became stuporous and lost the ability to speak. There had been a loss of weight of several pounds.

In the past he had always been in good health. During the past year he had been drinking heavily and once, nine months before admission, while intoxicated, he was beaten about the head by an unknown assailant. His neck had been stiff and painful for several years.

*Examination.*—At the time of admission the temperature was 98 F., the pulse rate 84, the respiratory rate 18 and the blood pressure 128 systolic and 78 diastolic. The patient was stuporous and aphasic. He sometimes understood simple spoken commands but at other times responded only to painful stimuli. Occasionally he muttered a single word or phrase. When left undisturbed, and even during the examination, he fell asleep. There was evidence of moderate loss of weight. The pupils were equal in size and reacted well to light and in accommodation and convergence. There was no papilledema. The patient did not notice objects in the left half of the visual field. Bilateral buccal and sucking reflexes were elicited. The neck was rigid, and attempts at flexion evoked pain. Examination of the heart, lungs and abdomen revealed nothing abnormal. The lymph nodes did not seem enlarged on palpation. The patient was too feeble to walk. The left arm was held in a flexed position and the left leg in extension; both extremities were spastic. There was left hemiparesis, affecting the face, arm and leg. The right arm and leg were rigid, being more so at some times than at others. No definite sensory loss was detected. Tendon reflexes were lively on both sides, being slightly more so on the left; the abdominal reflexes were absent, and the left plantar reflex was extensor and the right flexor in type. There was a forced grasping response in the left hand. The patient was incontinent of urine and feces.

*Laboratory Data.*—The white blood cell count was 5,900; the red blood cell count, 3,900,000, and the hemoglobin concentration, 78 per cent (Sahli). The urine showed a 1 plus reaction for albumin; the specific gravity was 1.021, and the sediment contained 6 to 8 red blood cells and an occasional white blood cell per high power field. The stool gave a positive reaction to guaiac. The cerebrospinal fluid was clear; there were no cells; the pressure was 150 mm.; the protein measured 160 mg. per hundred cubic centimeters; the colloidal gold curve was

0112232110, and the Wassermann and Davies-Hinton reactions were negative. A roentgenogram of the cervical portion of the spine showed marked evidence of hypertrophic arthritis.

*Course of Illness.*—The patient's general condition was unchanged during the first two weeks in the hospital. On the fourteenth day a ventriculogram showed upward displacement and partial obliteration of the midportion of the right lateral ventricle and displacement of both lateral ventricles and the third ventricle to the left.

The next day a craniotomy was performed in the right frontal region, and a tumor was noted deep in the substance of the right temporal lobe. The growth did not extend through the cortex to the meninges. It was fairly well demarcated and easily enucleated. The total

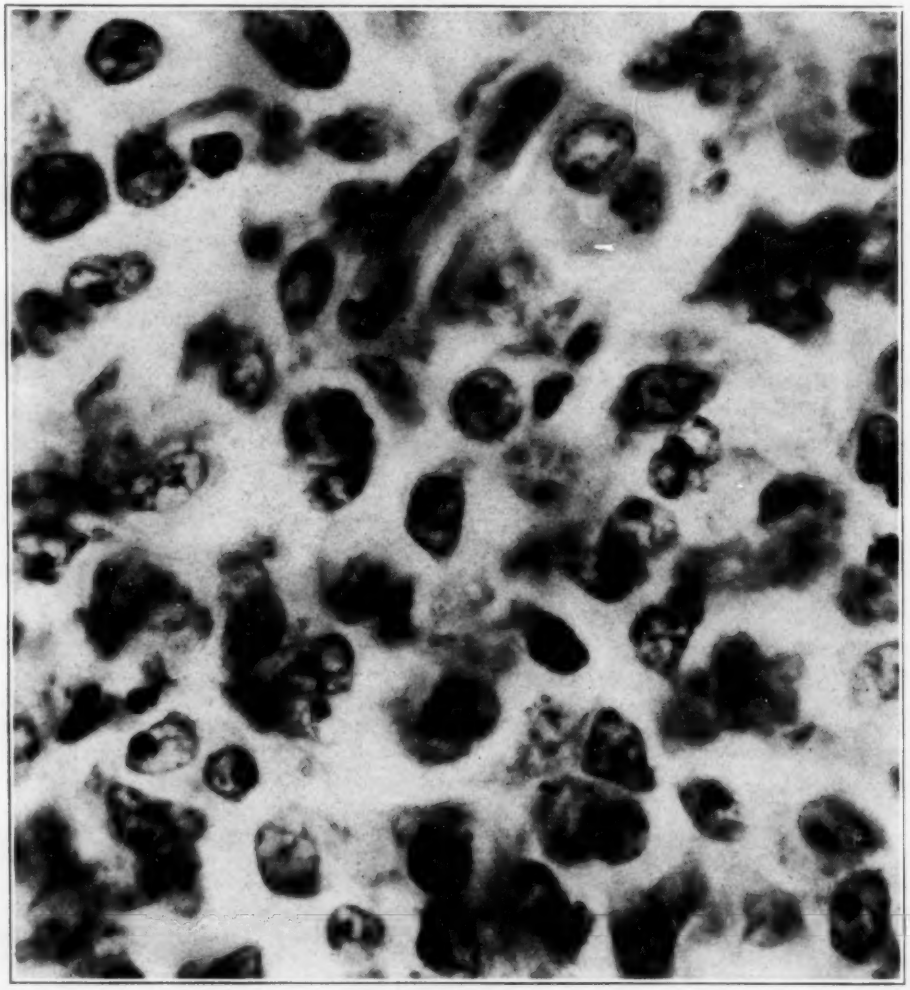

Fig. 4 (case 2).—Tumor cells showing pseudopod projections. Phloxine–methylene blue stain. × 750.

specimen weighed about 40 Gm. and was white, homogeneous and firm. The patient never regained consciousness after the operation. He died on the eight postoperative day, or the twenty-second day in the hospital.

*Postmortem Examination.*—The important pathologic changes were in the brain, lungs and cervical portion of the spine. Along the margins of the craniotomy opening, between the dura and the bone, was approximately 60 cc. of clotted blood. The medial surface of the right temporal lobe had been notched by the free edge of the tentorium. There was a large defect in the posterior and lateral surfaces of the right temporal lobe. Coronal sections disclosed a cavity in this lobe, presumably the former site of the tumor, measuring 6 by 4 by 4.5 cm. The tissues adjacent to the cavity were hemorrhagic. The superior, middle and inferior

temporal convolutions and the fusiform and hippocampal gyri, the lenticular nucleus, the external capsule and the claustrum had been destroyed on the right side. The body of the right lateral ventricle was pushed upward and obliterated. The third and both the lateral ventricles were displaced to the left. There was edema of the cerebral white matter for some distance surrounding the tumor. The convolutions of the frontal lobes were slightly atrophic.

Tissue was fixed in Zenker's fluid and in a 10 per cent concentration of solution formaldehyde U. S. P. and stained with phloxine–methylene blue, phosphotungstic acid hematoxylin and Laidlaw's reticulum stain and by Foot's modification of Hortega's stain for reticulum and Hortega's silver carbonate method for microglia.

Fig. 5 (case 2).—Characteristic arrangement of reticulum around individual cells. Foot's reticulum stain, × 750.

The tumor was grossly and microscopically identical with the one described in case 1 (figs. 4 and 5). Hortega's silver carbonate method for microglia revealed that many large cells, varying from small, activated microglia cells to large macrophages, were dispersed throughout the tumor (fig. 6).

The left lung weighed 1,020 Gm., and the right, 630 Gm. They were dark red and subcrepitant, and from the cut surface blood and frothy fluid could be expressed. The mucosa of the trachea and bronchi was red and covered with mucopurulent exudate. Microscopic examination showed bronchopneumonia and pulmonary congestion and edema. The bodies of the cervical vertebra were fused together ventrally by pronounced hypertrophic arthritic changes. At autopsy roentgenograms of the vertebrae and long bones revealed no evidence of tumor.

*Anatomic Diagnoses.*—The diagnosis was (1) reticulum cell sarcoma of the brain, involving the right temporal lobe, with a tentorial pressure cone and postoperative extradural hemorrhage on the right side; (2) hypertrophic arthritis of the cervical portion of the spine; (3) bronchopneumonia, involving the upper and middle lobes of the right lung, and (4) pulmonary congestion and edema.

The focal neurologic signs, i. e., the left hemiparesis, the reflex changes and the defects in the visual field were undoubtedly due to the tumor of the temporal lobe.

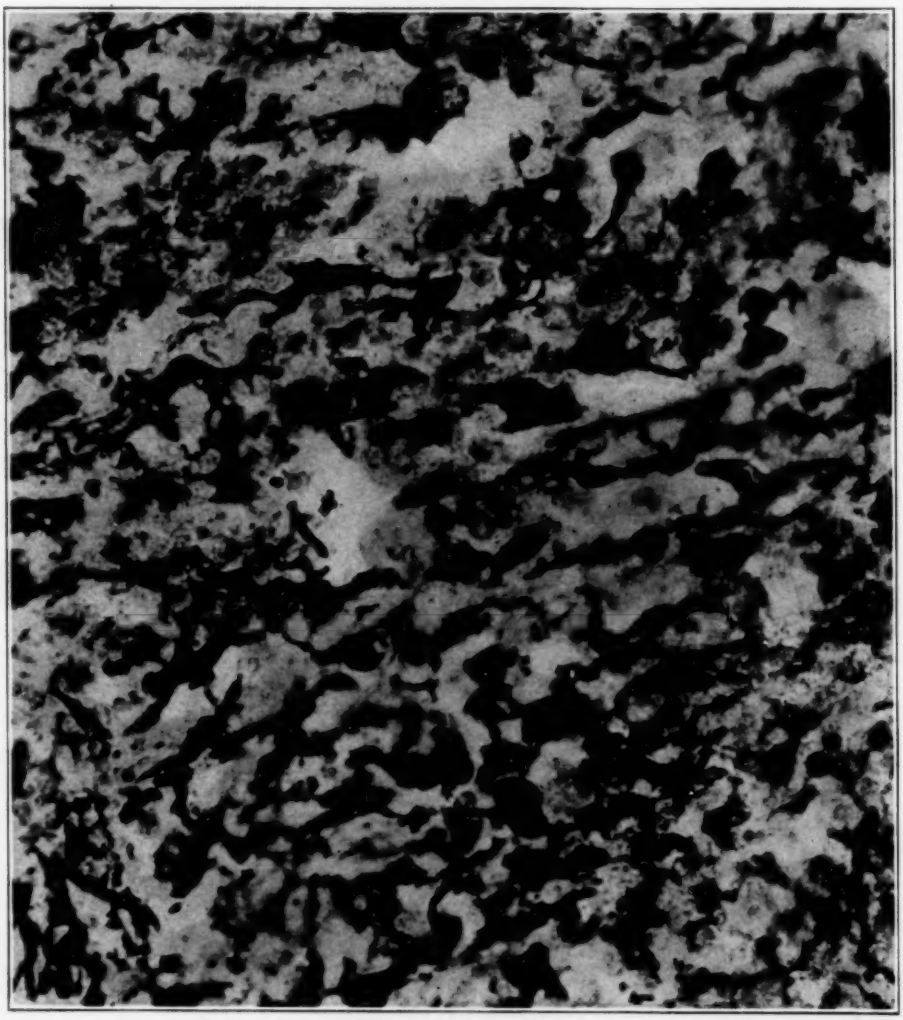

Fig. 6 (case 2).—Microglia cells within the tumor, many of which are approaching the form of macrophages. Hortega's silver carbonate stain for microglia. × 750.

The stupor, the sucking and grasping reflexes and the changing rigidity of the extremities could not be assigned to a single lesion. They indicated a widespread disorder of cerebral function, which may have been due either to an encephalopathic condition caused by chronic alcoholism and vitamin deficiency or, more likely, to the effects of increased intracranial pressure and the tentorial pressure cone. Gross and microscopic examination of the viscera, lymph nodes and bones disclosed no tumor elsewhere in the body.

COMMENT

*A. Characteristics of Reticulum Cell Sarcoma.*—Since one of the main purposes of this report is to establish that reticulum cell sarcoma may originate in the brain, it seems proper to recount briefly the characteristics of this type of tumor as it grows in other organs of the body and to show the resemblance of such a growth to the tumor arising in the brain.

That a tumor may arise from the reticulum cell was first suggested by Ewing [10] in 1913. In the early studies great significance was attached to the reticulum which surrounds these cells, hence the name reticulum cell sarcoma. This term is an unfortunate one, since there is no proof that reticulum is formed by these cells. In our opinion, the tumor cell resembles, and has a common origin with, the histiocyte, and the reticulum is formed by fibroblasts which are stimulated to activity by the tumor cells.

Reticulum cell sarcoma most often originates in the lymph nodes, and as a result is usually classified with the lymphomas. However, it has been described as arising in bone, the gastrointestinal tract, the lung, the thoracic wall, the thyroid, the ovary and the testicle. Such variation in the site of origin becomes understandable when it is realized that the type cell is the reticulum cell, or histiocyte, an element which occurs in any organ of the body.

Jackson [11] found the highest age incidence of reticulum cell sarcoma of the lymph nodes or of the generalized form to be in middle and late adult life; 84.5 per cent of all cases occurred after the age of 40 years. When the tumor arises in other organs, however, the age incidence is more variable, for reticulum cell sarcoma of bone appeared in younger persons, 77 per cent of the patients being less than 40 and 35 per cent less than 20 years of age.[12]

The tumor grows rapidly and is highly invasive, but despite the gross and microscopic appearance of malignancy, it may remain localized for long periods. Thus, Parker and Jackson [12] found the life span of patients with reticulum cell sarcoma of bone to be six months to fourteen years. Some patients did surprisingly well, even though surgical removal was delayed for a year or more. The tumor seems to spread locally and along lymph vessels, but at any time may set up distant, blood-borne metastases.

The gross appearance of reticulum cell sarcomas has been remarkably similar, whatever their site of origin. The tumor is white or gray-pink, firm in consistence and homogeneous or slightly granular in appearance. It resembles "fish flesh."

The histologic characteristics are as follows: The tumor is exceedingly cellular; the cells are uniform in shape and size and measure from 12 to 15 microns in diameter. The typical nucleus is round or oval and vesicular, with fine, widely dispersed nuclear chromatin. The nucleolus is inconspicuous except in anaplastic tumors, in which it is apt to be prominent. The cytoplasm is variable in quantity, takes a faint eosinophilic stain and may show pseudopods, indicative of ameboid activity. There may be few or many mitotic figures. Necrosis and fibrosis are uncommon, and when the former is present, it is of the infarct type. Eosinophils do not occur as a rule. Special stains for reticulum disclose delicate strands which surround individual cells and groups of cells. This network constitutes the stroma of the tumor. The vascularity is not great.

10. Ewing, J.: Endothelioma of Lymph Nodes, J. M. Research **28**:1-40, 1913.

11. Jackson, H., Jr.: The Classification and Prognosis of Hodgkin's Disease and Allied Disorders, Surg., Gynec. & Obst. **64**:465-467, 1937.

12. Parker, F., Jr., and Jackson, H., Jr.: Primary Reticulum Cell Sarcomas of Bone, Surg., Gynec. & Obst. **68**:45-53, 1939.

*B. Characteristics of the Primary Sarcoma of the Brain Which We Assert to Be of the Reticulum Cell Type.*—Including the 2 cases presented in this paper, a total of 7 cases of a tumor which we believe to be primary reticulum cell sarcoma of the brain have been reported (table 1).

The average age of the patients in this series was 44 years, with a range from 9 to 72 years. All the tumors occurred in males, a fact for which we have no explanation other than that of pure coincidence. This age incidence in general is in agreement with that of primary reticulum cell sarcoma of lymph nodes.

The average duration of symptoms prior to operation was approximately six months. This short preoperative course is suggestive of metastatic carcinoma or

*Summary of Cases of Reticulum Cell Sarcoma of Brain Verified by Autopsy*

| Author | Age, Yr.; Sex | Survival Time, Mo. | Symptoms | Signs | Location | Gross Appearance | Microscopic Appearance |
|---|---|---|---|---|---|---|---|
| Bailey..... | 45 M | 14 | Headache; convulsions; aphasia | Papilledema; left hemiparesis | Right temporal lobe | No gross description | Small round cell with moderate cytoplasm; abundant reticulum; perivascular tumor cells |
| Ferens..... | 36 M | 16 | Headache; nausea and vomiting | Papilledema; right hyperreflexia | Left temporal lobe | Gray-red; firm; adherent to dura | Cells resembling histiocytes; abundant reticulum; perivascular tumor cells |
| Benedek.... | 34 M | 1 | Headache; failing vision | Right hemiparesis | Left temporal lobe | Yellow-pink; homogeneous | Cells resembling microglia cells; abundant reticulum |
| Yuile..... | 50 M | 1 | Headache and drowsiness | Left hemiparesis | Right temporal lobe | Gray-pink; firm | Cells 12-14 microns in diameter; many mitoses; cells resembling microglias; abundant reticulum; perivascular tumor cells |
| Hsu..... | 9 M | 6 | Headache; loss of memory; diplopia | Papilledema; palsy of right side of face; dysarthria | Left temporal lobe | "Fleshy"; rubbery consistence; hemorrhage and necrosis | Round and oval cells; abundant reticulum; perivascular tumor cells |
| Kinney and Adams | 72 M | 6 | Headache and irritability | Confusion; left hemiparesis | Right temporal lobe | Firm; pink-gray; homogeneous | Cells 12-14 microns in diameter; ameboid activity; abundant reticulum; perivascular tumor cells |
| Kinney and Adams | 66 M | 3½ | Headache and fatigability | Stupor; aphasia; right hemiparesis | Left temporal lobe | Firm; pink-gray; homogeneous | Cells 12-14 microns in diameter; ameboid activity; abundant reticulum; perivascular tumor cells |

glioblastoma multiforme, clinical diagnoses which were considered in each of our 2 cases. The period of survival after operation varied from three weeks to one and a third years, with an average of about three months.

The symptoms by which the tumor manifested itself were remarkably uniform, owing to the constancy of its anatomic location in the temporal lobe. Headache was a conspicuous and early symptom in every case, even when the intracranial pressure was not elevated. Mental disturbances constituted a regular symptom and included in the later stages changes in character, drowsiness, inattentiveness, irritability and confusion. Hemiparesis usually appeared late, and when the dominant cerebral hemisphere was involved, there was partial global aphasia. Judging from the short duration of the illness and the gross and microscopic appearance of the tumors, growth was rapid. Invasion of the brain followed the lines of least resistance, a tendency which probably accounts for the spread along the Virchow-

Robin spaces. In none of the cases were the meninges grossly involved. The duration of life in these cases was observed to be shorter than that in cases in which the tumor occurred in other organs of the body, but this was undoubtedly due to their location. One patient, however, survived for one and a third years after operation, before his death from a recurrence of the tumor.

The gross appearance of primary reticulum cell sarcoma of the brain did not differ in any way from that of reticulum cell sarcoma in other organs. The tissue was firm, even elastic at times, was homogeneous and varied from white to gray-pink. There were no areas of necrosis, cysts or hemorrhages. The central and convolutional white matter adjacent to the tumor was edematous. Distortion of the ventricular system, tentorial pressure cone and other signs of swelling of the brain were found in 3 of the 6 cases.

The histologic picture of these tumors was such that they were identified as reticulum cell sarcoma with no great difficulty. The type cell appeared the same; the delicate stroma of reticulum surrounded individual cells; numerous cells, differentially stained as microglial phagocytes or macrophages, were abundant throughout the tumor; tumor cells growing in walls of veins were seen, and there were no tumor giant cells. In recapitulation, this group of tumors of the brain conformed in every detail to the pathologic entity now generally accepted as reticulum cell sarcoma. Careful autopsy in each case failed to show any sign of primary tumor in other organs which could have given rise to cerebral metastases. Thus, the cerebral origin is established beyond doubt.

*C. Relation of Primary Reticulum Cell Sarcoma of Brain to Microglioblastoma.*—Until fairly recently it has been the consensus that microglia cells do not undergo neoplastic change. In 2 of the cases in this group the tumor was reported as microglioblastoma. The histologic diagnosis in each instance was established by the presence of large numbers of microglial phagocytes which were widely disseminated through the substance of the tumor. The presence of such cells is not in itself sufficient basis for diagnosis unless it is proved that these microglia cells are the tumor cells, since Penfield [13] demonstrated similar microglial phagocytes in gliomas, though not in the same numbers as in our 2 cases. However, the fact that the majority of the tumor cells were not microglial phagocytes and were not stained by Hortega's silver carbonate method should make one hesitant in classifying such a tumor as microglioblastoma.

On the other hand, it is generally agreed that the reticulum cell sarcoma is a malignant tumor which stems from either the reticulum cell or the histiocyte and, further, that in the central nervous system there are two representatives of this cell series, the meningeal, or perithelial, histiocyte and the microglia. Theoretically, either could give rise to a reticulum cell sarcoma. The proof of this must await embryologic evidence as to the exact origin of the microglia. We are inclined to a more conservative view, which classifies this tumor as reticulum cell sarcoma and leaves the matter of microglioblastoma versus meningeal histiocytic sarcoma an unsettled question.

One intriguing explanation of the preponderance of these tumors in the temporal lobe is worth mention. The microglia cells, derived probably from meningeal histiocytes, invade the brain from certain fixed points, among which is the tela choroidea. It is quite possible that tumors from this group of cells arise from these same points and that the tela choroidea of the temporal horn of the lateral ventricle

13. Penfield, W.: Microglia and the Process of Phagocytosis in Gliomas, Am. J. Path. **1**:77-89, 1925.

is the site of origin. Support for this hypothesis would be provided by the observation of similar tumors arising from the tela choroidea of the third and fourth ventricles and the cerebral peduncles. It is interesting to note that the tumor in 1 of Hsü's cases which he called alveolar sarcoma, and which Bailey (in a personal communication) stated to be identical with the tumor in our case 2 arose in the cerebellum. Further confirmation of this hypothesis must await the report of additional cases.

SUMMARY

Two cases of a primary tumor of the temporal lobe identical in every respect with reticulum cell sarcoma occurring in other organs of the body are presented, with complete autopsy reports. The tumors in these 2 cases were similar to those in 5 other cases which have been reported under the names perithelial sarcoma, microglioma, microglioblastoma and reticulum cell sarcoma.

The clinical syndrome in these cases was uniform, owing to the constancy of the anatomic site of the tumor in the temporal lobe. The chief symptoms were headache, mental deterioration, hemiparesis and aphasia (left-sided lesions). The average age was 44 years.

Grossly, the tumors consisted of firm, gray-pink, homogeneous tissue, which widely invaded the central white matter of the temporal lobes. Microscopically, they appeared very cellular, and the tumor cells were oval, with moderate to abundant cytoplasm and vesicular nuclei. The stroma consisted of reticulum encircling individual cells. Ameboid activity of the tumor cells was conspicuous. Tumor giant cells did not occur.

The opinion is expressed that these tumors are derived from primitive reticulum cells, the progenitor of the meningeal histiocyte, or microglioblast, and represent a distinct type of malignant mesodermal tumor of the brain.

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# ATHEROSCLEROTIC MYELOPATHY WITH SYRINX FORMATION

## DIFFERENTIATION FROM OTHER TYPES OF SYRINGOMYELIA

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Atherosclerotic myelopathy is rare. In a previous report, Keschner and Davison [1] described 2 cases of atherosclerosis of the spinal vessels with myelopathic changes; these were encountered within a period of six years in a series of about 200 cases of cerebral arteriosclerosis in which necropsy was performed. Since then, in a period of ten years, about 700 additional cases of cerebral arteriosclerosis have been observed. In a number of these cases atherosclerotic myelopathy was presented, in 2 of which cavities in the spinal cord comparable to those occurring in syringomyelia were noted. It is well known that the most common causes of syringomyelic cavities are: (1) destruction of tissue of the cord by an intramedullary tumor; (2) circulatory interference within the cord due to compression of intraspinal vessels by an intramedullary tumor, and (3) circulatory interference due to direct compression of the cord and its vessels by thickened meninges or by an extramedullary neoplasm or by both (Keschner and Davison [1]). In some cases the pathologic process may be due to more than one of these factors. Atherosclerosis of the intraspinal vessels may occasionally lead to destruction of tissue with formation of a syrinx and no glial replacement. Sometimes such a cavity, as shown in case 1 in the present study, may become surrounded by a wall of connective tissue. This type of cavity, as well as those previously enumerated, should not be confused with that of so-called true syringomyelia, which is the result either of a congenital developmental anomaly of the cord, with dilatation of its central canal, or of central gliosis, the latter being due to the activity of glial or ependymal cells, which may proliferate under various circumstances.

### REPORT OF CASES

CASE 1.—W. J., a man aged 47, was admitted to the Montefiore Hospital on May 6, 1921 with a history of slight "cutting" pains in the left shoulder and a feeling of heaviness in the right arm. The right arm became paretic. About three months later the patient complained of a feeling of "weight" in the right calf; this later involved also the left leg. Diminution of power in the lower extremities soon followed. Later, the patient described a "heavy feeling" in the abdominal muscles and "jumping" sensations in the muscles of the legs.

*Physical and Neurologic Examination.*—Examination disclosed kyphosis of the dorsal portion of the spine; spastic gait; some atrophy of the muscles of the hands and forearms, and pronounced atrophy and fibrillation of the muscles of the upper portions of the arms and the shoulder girdles, including atrophy of the supraspinati and infraspinati muscles. Power was somewhat diminished in the muscles of the left arm and greatly reduced in the muscles of

From the Neuropsychiatric Service and the Neuropathological Laboratory of the Montefiore Hospital for Chronic Diseases.

1. Keschner, M., and Davison, C.: Myelitis and Myelopathic Lesions: III. Arteriosclerotic and Arteritic Myelopathy, Arch. Neurol. & Psychiat. **29**:702 (April) 1933.

the right arm. Tonus was increased in all muscle groups, although to a lesser degree in the muscles of the upper extremities. The biceps, ulnar and radial reflexes were absent on both sides. The deep reflexes of the lower extremities were greatly increased, with ankle clonus and a Babinski toe sign bilaterally.

Appreciation of the sense of pain was lost over the face and body down to the sixth thoracic segment. Cold was not perceived over the face and trunk and the upper extremity down to the fourth thoracic dermatome on the left side and to the seventh on the right side. Appreciation of heat was lost on the face and body down to the third thoracic segment on the left side and to the first lumbar segment on the right side. Tactile sense was intact; vibratory sense was lost below the clavicular level; postural sense was defective. Stereognosis and two point discrimination were intact.

Examination of the cranial nerves revealed that the left eyeball was somewhat prominent and the palpebral fissure on the left was narrow. The left pupil was slightly smaller than the right; both were regular and reacted to light and in accommodation. There was hypalgesia of the cornea of the left eye.

*Laboratory Data.*—The Wassermann reactions of the blood and the spinal fluid were negative. Examination of the spinal fluid revealed 3 cells per cubic millimeter and a total protein of 31.8 mg. per hundred cubic centimeters. The blood counts and chemical constituents of the blood were normal. There was a faint trace of albumin in the urine, with occasional hyaline and granular casts.

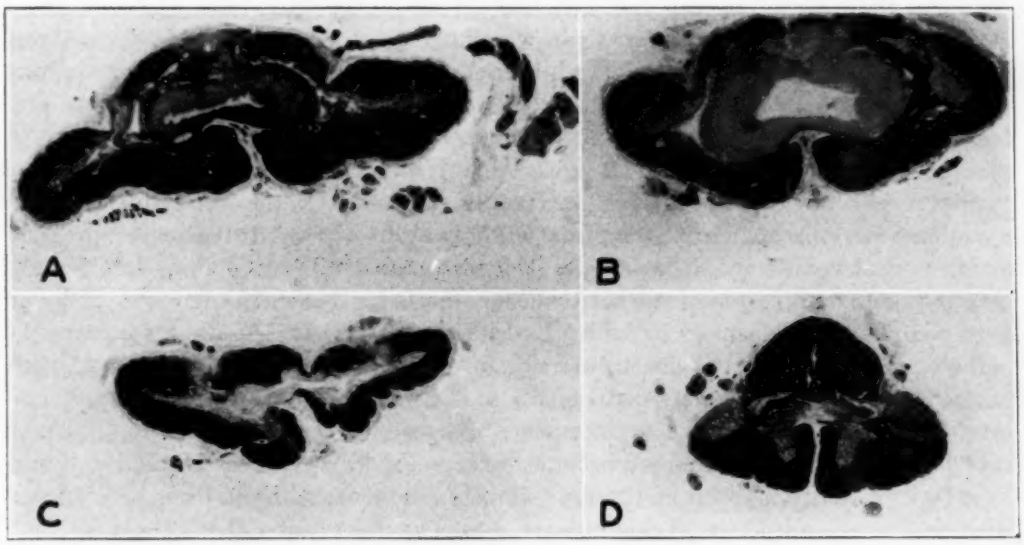


Fig. 1.—Sections of the spinal cord from the cervical to the lower thoracic region. Note the extensive cavities in the cervical region (*A* and *B*), surrounded by a pale gray area formed by parts of the posterior columns, the gray matter and part of the crossed pyramidal tracts (*A* and *B*). In the upper thoracic region (*C*) there are distortion and partial demyelination of the posterior columns and a cavity on the right side. In the lower thoracic region (*D*) there is merely descending demyelination of the crossed pyramidal tracts. Myelin sheath stain.

*Course.*—There was relentless progression of symptoms. In the past ten years the lower extremities had become spastic. Shooting pains in the legs and girdle pain on the right side of the abdomen became more intense; fibrillary twitchings in the muscles of the shoulder, chest and arm on the right side also became more pronounced. During the past five or six years, because of the loss of thermal sense, the patient had frequently sustained burns on his upper extremities. A résumé of the neurologic examination in 1936 made it evident that the major lesion was in the cervical portion of the cord, involving the pyramidal tract, posterior column, spinothalamic tracts and anterior horn on both sides. The sensory disturbances were of the dissociated type. The patient received high voltage roentgen therapy to the spine, with relief of pain. On Feb. 26, 1941 he had an acute and fatal attack of coronary thrombosis.

*Gross Examination.*—Brain: The pia-arachnoid was thickened and had a slightly dull appearance but stripped easily. The pacchionian granulations were prominent. There were

agonal hemorrhages in the region of the motor and premotor convolutions. The vessels at the base, especially the internal carotid and middle cerebral arteries, presented marked atherosclerosis. There was a small area of softening in the region of the inner segment of the globus pallidus.

Spinal Cord: The cord was thinned throughout its extent. The central canal was dilated, with considerable thinning out of the posterior columns from the cervical to the lower thoracic segments (fig. 1).

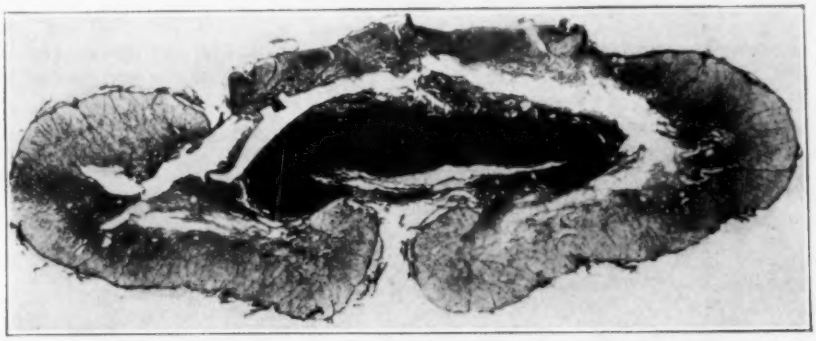

Fig. 2.—Section of the cervical region. Note the extensively thickened, dark mass of connective tissue surrounding the cavity. Holzer stain.

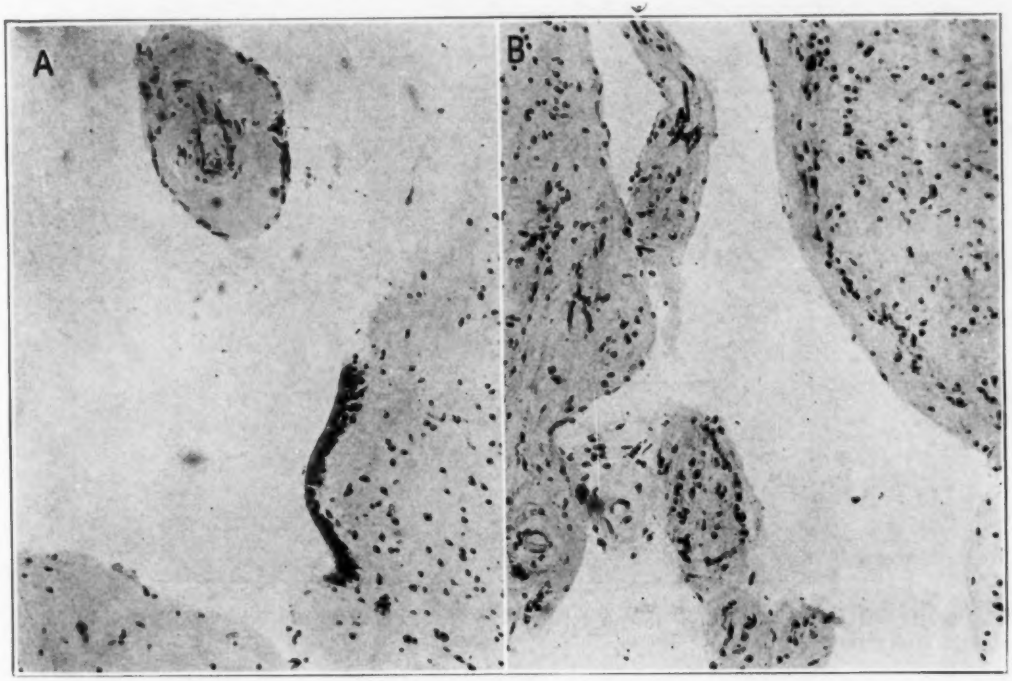


Fig. 3.—*A*, cavity, partially lined by ependymal cells, and a severely hyalinized vessel with a narrow lumen.

*B*, hyalinization and proliferation of vessels in the wall of the cavity, with absence of ependymal lining. Cresyl violet stain; × 66.

*Microscopic Examination.*—Sections of the cortex, diencephalon, pons, medulla oblongata and spinal cord in this case, and in the next case, were stained by the myelin sheath method and with cresyl violet. Sections of the spinal cord were also stained by the Spielmeyer, sudan III, Holzer, Van Gieson and Bielschowsky methods.

Cortex: Except for moderate atherosclerosis of the cortical vessels, no abnormalities were noted.

Basal Ganglia: The myelin sheath preparation showed a cystic area between the first and the second segment of the pallidum. The myelin sheaths in this region had undergone various types of pathologic change. In the cresyl violet preparation, the cyst wall was seen to contain a few vascular channels, compound granular corpuscles, some of which contained pigment granules, fibroblasts and endothelial cells. The involved ganglion cells in this region also revealed various pathologic changes. The vessels, too, presented evidence of atherosclerosis.

Pons and Medulla Oblongata: This region presented no abnormalities.

Spinal Cord: Most of the cervical and upper thoracic segments were flattened; the posterolateral tracts were greatly shrunken. There was a cavity in the lower cervical region (fig. 1 *A* and *B*). In the myelin sheath preparation this was seen to be surrounded by a dense,

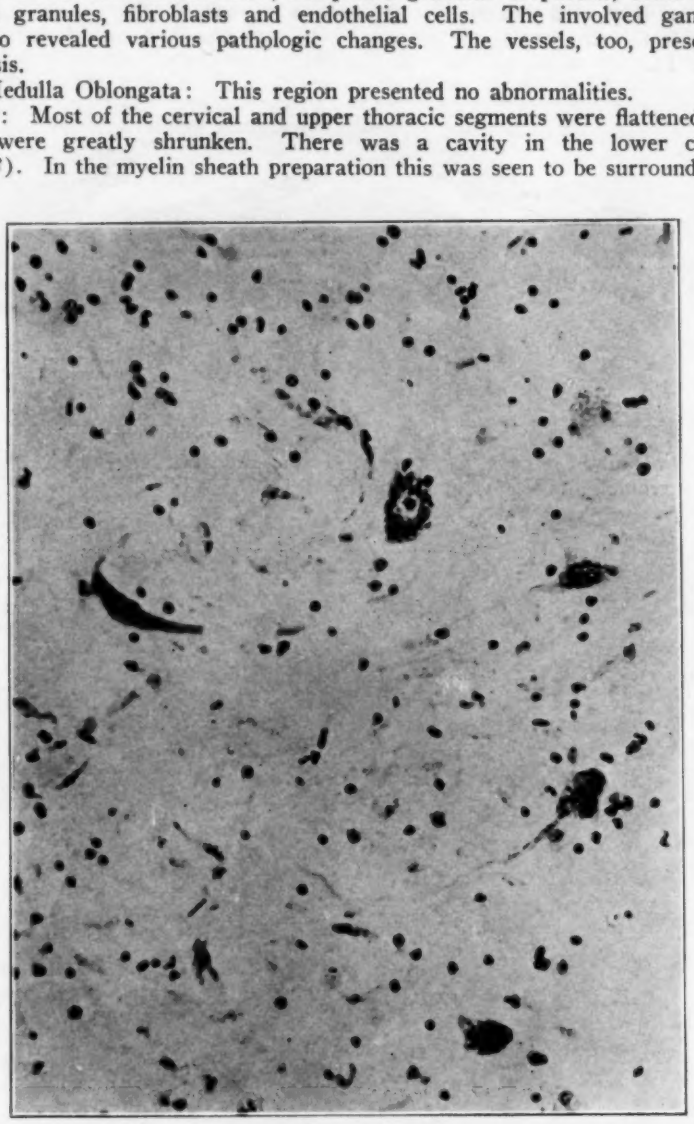

Fig. 4.—Diminution in number of anterior horn cells, disintegration, shrinkage and pyknosis. Cresyl violet stain; × 200.

pale area, formed by parts of the posterior columns, the gray matter and part of the crossed pyramidal tracts (fig. 1 *A* and *B*.). Sections of the upper cervical segments disclosed pronounced demyelination of the posterior columns and the crossed pyramidal tracts and thinning of the gray matter. In sections below the cavity, the cord at the upper thoracic segments was thinned, the posterior columns being especially affected; the gray matter was conspicuously shrunken. A cavity lay on the right side in the upper thoracic region (fig. 1 *C*). Sections of the lower thoracic and the lumbar region merely disclosed a descending demyelination of the crossed pyramidal tracts (fig. 1 *D*). The cavity in the posterior columns in the cervical region did not communicate with the central canal. The myelin sheaths in the destroyed area had almost entirely disappeared, though here and there a few myelin fibers could be identified. At the periphery of the area of complete demyelination, the myelin sheaths and

axis-cylinders showed various types of pathologic change, such as fragmentation, swelling, variation in size and corkscrew processes. The sudan III preparation revealed no fatty deposits in the demyelinated areas, but numerous thickened vessels with conspicuous hyaline degeneration could be seen. The few remaining anterior horn cells contained lipid deposits. The Holzer preparation showed an extensive dense, bluish area around the cavity, with fibers running in all directions (fig. 2); these processes were not typical glial fibers but took a reddish stain in the Van Gieson preparation; they were readily identified as connective tissue. In the cresyl violet preparation the cavity was noted not to be in direct communication with the central canal. The usual ependymal rests were observed and were noted to be independent of the cavity. In some areas, a few ependymal cells were present near the cavity (fig. 3 *A*). The area surrounding the cavity was filled with fibroblasts and a few

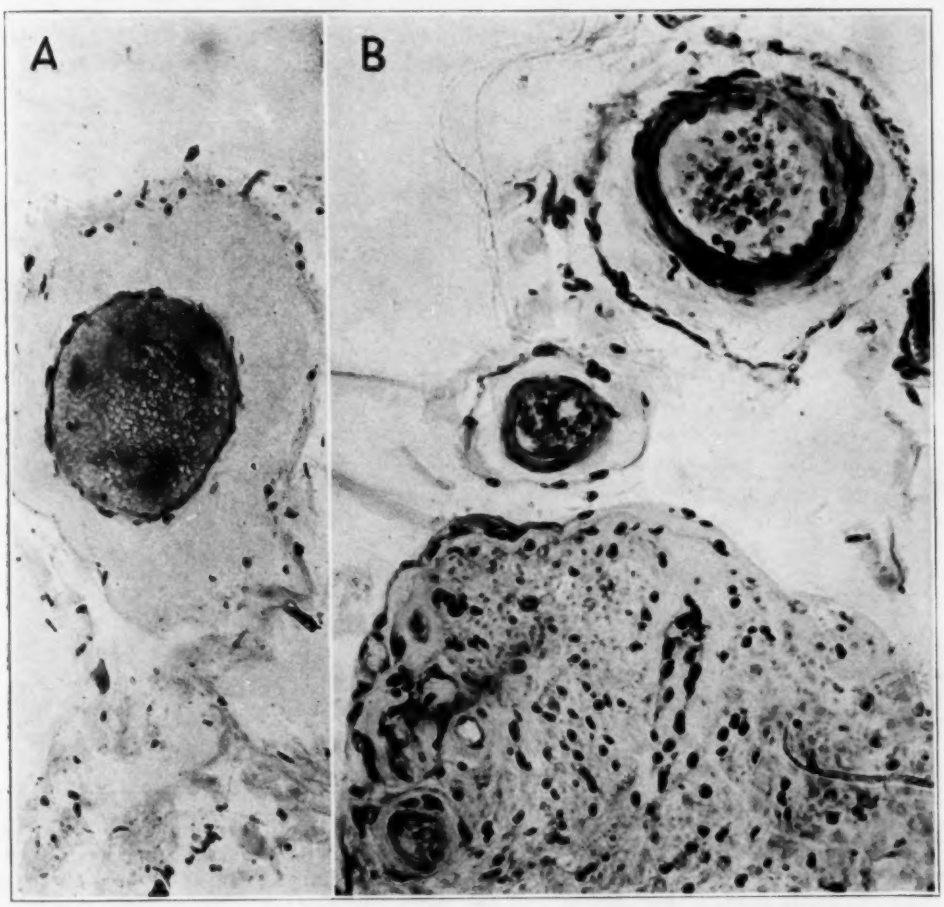


Fig. 5.—*A*, hyalinized vessel and thrombosis in the meninges. *B*, hyalinized and atherosclerotic vessels in the meninges and roots. Cresyl violet stain; × 200.

glial cells of the microglia and astrocyte variety; there were numerous hyalinized vessels with narrow lumens (fig. 3 *A* and *B*), and proliferation of vessels was sometimes seen (fig. 3 *B*). The anterior horn cells were diminished in number. Some of the cells were pyknotic and shrunken; others were completely disintegrated (fig. 4). Hyalinized vessels were also noted in the gray matter and in the region of the meninges (fig. 5 *A*), and even in the roots in sections of the cord below the cavity (fig. 5 *B*). In sections of the lower thoracic and the lumbosacral region, the central canal was represented by clusters of ependymal cells without any cavity.

This case at first presented a difficult diagnostic problem. Most observers expressed the belief that the process was syringomyelia. The duration of the illness and the dissociated sensory disturbances favored such a diagnosis. Histopathologic

study, however, disclosed atherosclerosis of the intraspinal and some of the extraspinal vessels, including those of the meninges and roots. The process in the cord was of long duration and finally led to cavitation. Cavitation has also been reported in some instances of so-called subacute necrotic myelopathy by Foix and Alajouanine,[2] Greenfield and Turner[3] and others. As in some of the cases reported by these authors, the outstanding process in the present case was atherosclerosis and hyalinization of the spinal vessels. That this case was not an instance of true syringomyelia was indicated by the nature of the tissue around the cavity. This proved to be connective, and not glial, tissue. Our case differed from the cases reported by the aforementioned authors in the long duration of the illness (sixteen years). Keschner and Davison[1] previously reported 2 cases of atherosclerotic myelopathy in which similar conditions occurred without cavitation.

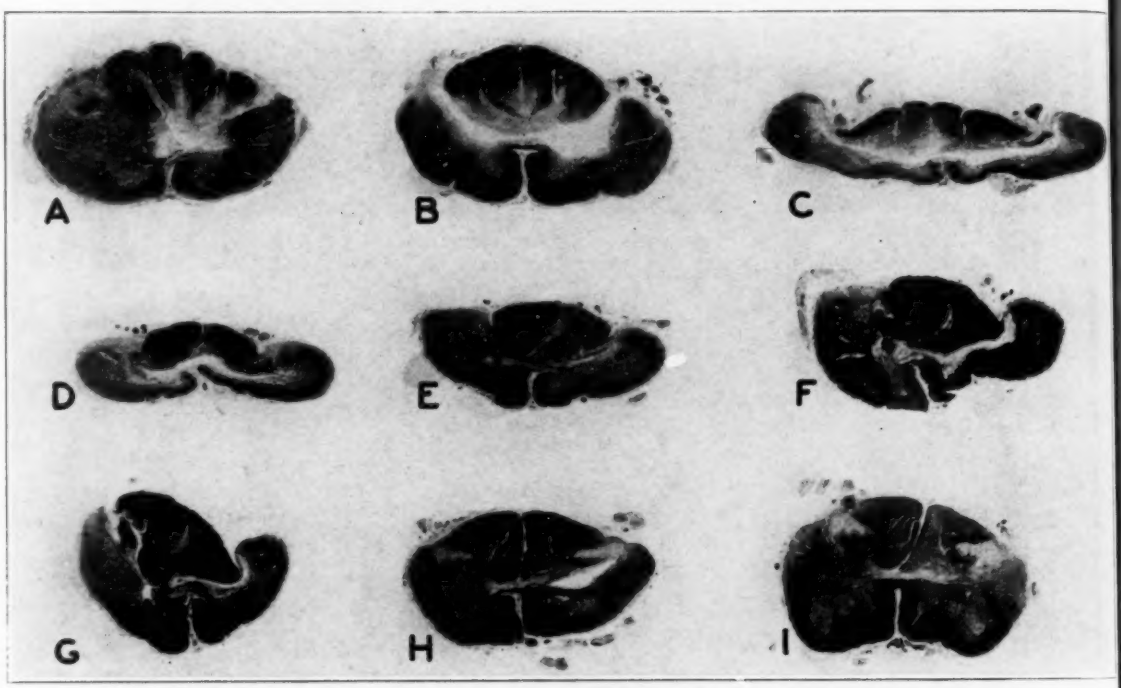


Fig. 6.—Transverse sections of the spinal cord at various levels, showing a cavity extending from the cervical to the thoracic region, most noticeable in the cervical and upper thoracic regions (*B*, *C* and *D*). A small cavity lies in the left lumbar region (*H*). There were destruction of the gray matter and partial destruction of the posterior columns and crossed pyramidal tracts (*B*, *C* and *D*). Myelin sheath stain.

Case 2.—M. B., a woman aged 67, was admitted to the Montefiore Hospital on March 9, 1939. For twenty-five years she had been unable to move her arms above her head. Eighteen years before admission she had been operated on for a pelvic condition and at that time had been unable to void for eight days; she had had incontinence of feces and urine ever since. About twelve years before her entrance to the hospital an ill defined pain appeared in the back and became constant. She had fainting spells beginning fifteen years before, associated with inability to walk. About three and a half years prior to admission the patient noted that fainting spells were associated with pains in the left leg and arm and with a sensation of a burning needle piercing the left side of the head. She had also experienced

2. Foix, C., and Alajouanine, T.: La myélite nécrotique subaiguë, Rev. neurol. **2**:1, 1926.

3. Greenfield, J. G., and Turner, J. W. A.: Acute and Subacute Necrotic Myelitis, Brain **62**:227, 1939.

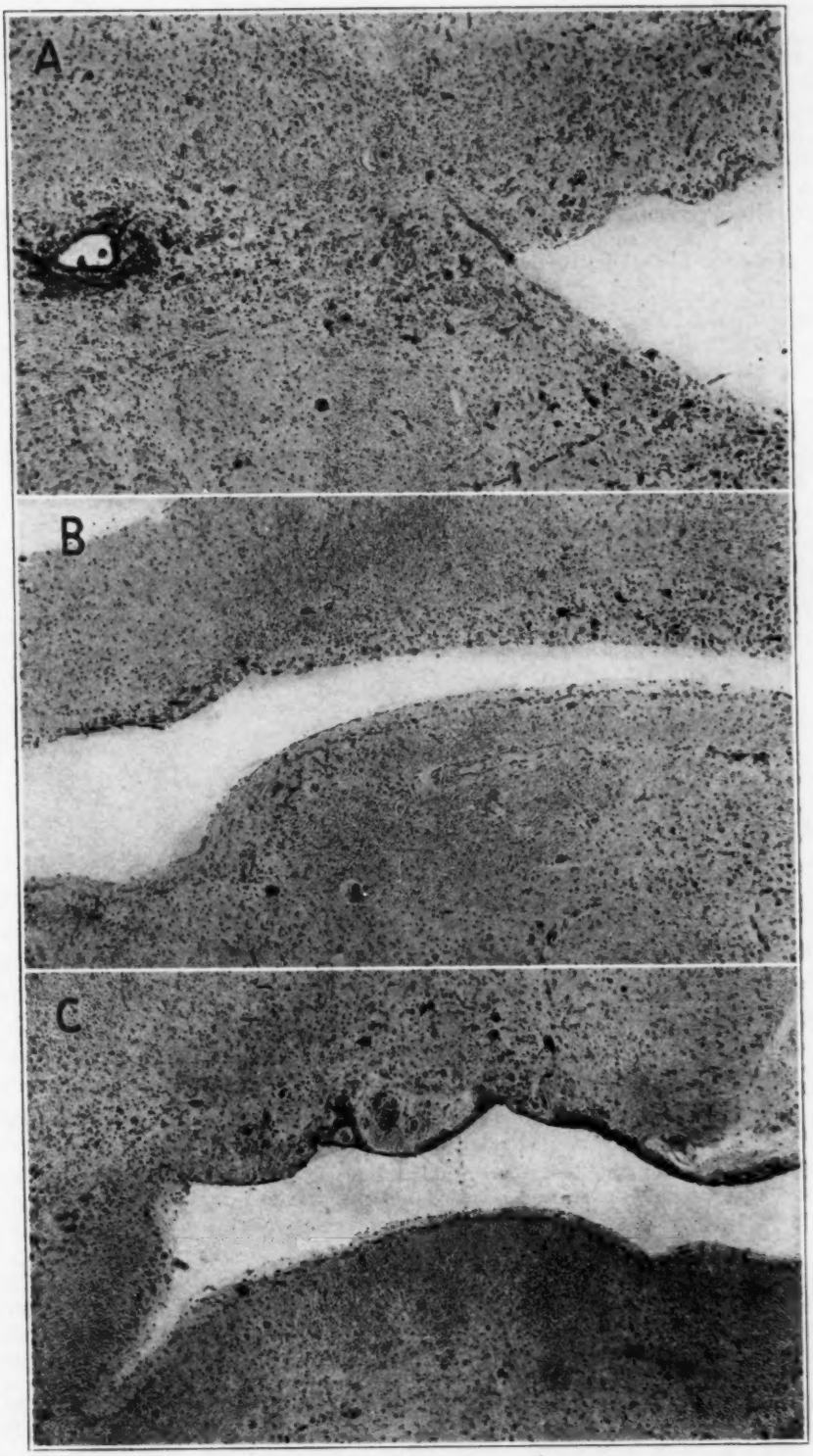


Fig. 7.—Separation of the central canal from the cavity (*A*), absence of ependymal lining in the cavity (*B*) and fusion of the cavity with the central canal, evident in one section, the cavity being partially lined with ependymal cells (*C*). Cresyl violet stain; × 30.

numbness of the left side of the body for the past ten years. Impairment of memory for the preceding two or three years suggested involvement of the brain.

*General and Neurologic Examination.*—There was extreme tenderness over the entire spinal column. Varicosities were present in both legs. Atherosclerosis of the peripheral vessels was evident. The patient walked slowly and on a wide base and used her arms in balancing. Strength was fair in the upper and lower limbs, and there were no muscular atrophies. The deep reflexes were absent in the upper extremities but were active and equal in the lower extremities. The abdominal reflexes were absent. There were no pathologic reflexes. Sensation was impaired over the left side of the body below the second cervical dermatome, pain and temperature sensation being involved more than the touch sense. The fundi showed sclerotic vessels; the cranial nerves were normal. The patient was somewhat circumstantial, but the stream of her mental activity was relatively clear and coherent.

*Laboratory Data.*—The blood count was normal, and the Wassermann reactions of the blood and the spinal fluid were negative. The urine showed a trace of albumin, 15 to 20 pus cells per cubic millimeter and occasional epithelial cells. Examination of the spinal fluid showed 2 cells per cubic millimeter, no globulin, 34 mg. of protein per hundred cubic centimeters and a normal colloidal gold curve. A roentgenogram of the cervical portion of the spine revealed nothing abnormal.

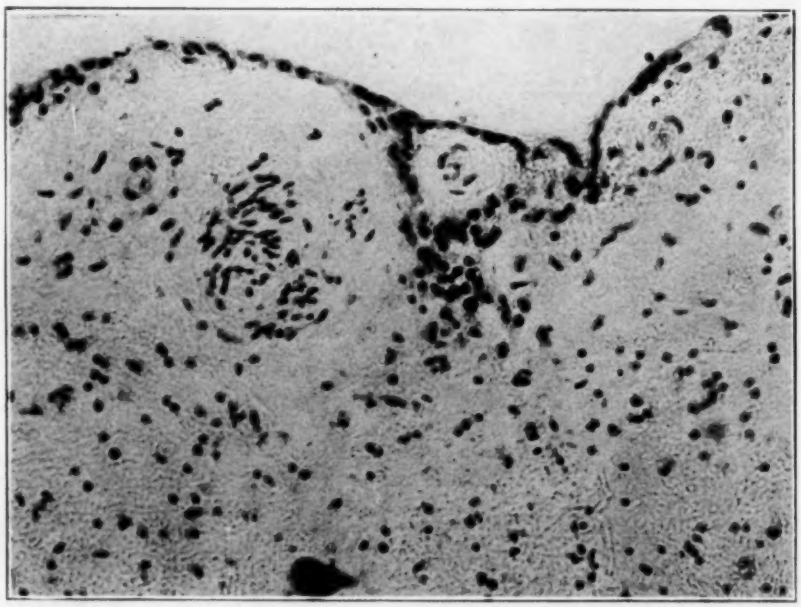

Fig. 8.—Hyalinization and proliferation of vessels near the cavity. The cavity, which is the same as that shown in figure 7, is partially lined with ependymal cells. Cresyl violet; × 200.

*Course.*—A tumor of the lower cervical portion of the cord was suspected, but roentgenographic and manometric studies revealed nothing significant. Because of the dissociated sensory disturbances, syringomyelia was considered as the most likely diagnosis. The patient died of coronary occlusion on March 28, 1939.

*Gross Examination.*—Brain: The frontal convolutions showed slight atrophy. The vessels at the base presented marked atherosclerotic changes; the basilar and vertebral arteries had a "goose neck" appearance. There was uniform dilatation of the entire ventricular system, including the aqueduct of Sylvius and the fourth ventricle. The corpus callosum and other commissures were thinned.

Spinal Cord: The cord was shrunken and contained an extensive cavity in the cervical region (fig. 6 *B* and *C*). The fiber tracts surrounding the cavity formed a thin shell (fig. 6 *C* and *D*). The bulk of the white matter about the cavity was destroyed. All that could be seen was a rim of ventrolateral tracts surrounding the posterior column; this was especially true of the cervical and upper thoracic regions (fig. 6 *C* and *D*).

*Microscopic Examination.*—Cortex: Sections disclosed shrinkage of the white matter and occasional destruction of myelin sheaths. Most of the vessels of the cortex and the white

matter showed extensive atherosclerotic changes, namely, thickening and proliferation of the intima, fenestration, deposits of cholesterol and splitting of the lamina elastica. These changes were most conspicuous in the larger vessels, such as the basilar and the posterior cerebral artery. There was no distortion in the arrangement of the cytoarchitectural layers. Occasional collections of compound granular corpuscles were noted in the perivascular spaces of some of the smaller vessels.

Spinal Cord: In the myelin sheath preparations, a cavity extended from the cervical to the thoracic region of the cord, involving most of the gray matter and part of the white matter (fig. 6); the cavity was most prominent in the cervical and upper thoracic regions (fig. 6 *B*, *C* and *D*). A small cavity was also present in the left lumbar region (fig. 6 *H*). In sections through the cervical region the cord was flattened out. There were destruction of the gray matter and partial destruction of the posterior columns and the crossed pyramidal tracts (fig. 6 *B*, *C* and *D*). The myelin sheaths and axis-cylinders of these tracts showed various types of pathologic change. In the cresyl violet preparations the central canal was separated from the cavity (fig. 7 *A*), and the latter was not lined by ependymal cells (fig. 7 *A* and *B*). In one section, however, there was fusion of the cavity and central canal; the cavity in this instance was partially lined by ependymal cells (fig. 7 *C*). In some regions the wall of the cavity contained compound granular corpuscles. The vessels of the gray matter, especially near the cavity, showed conspicuous atherosclerotic changes and hyalinization (fig. 8). The vessels of the meninges in these regions also presented atherosclerotic changes. In some sections of the cervical portion of the cord there was extensive destruction of the anterior horn cells. However, in most of the other regions these cells were well preserved.

This case is somewhat similar to the previous one, especially in regard to the long duration of the illness. As in the first case, the clinical diagnosis was syringomyelia. The histopathologic process in the cord indicated that the lesions were the result of atherosclerosis. In contrast to case 1 and to some of the cases reported by Foix and Alajouanine [2] as instances of "subacute necrotic myelopathy," there was little connective tissue reaction. The products of disintegration in case 2 were removed without replacement by glial or connective tissue.

## COMMENT

Henneberg [4] described arteriosclerotic lesions in the cord and included such senile changes as were observed in cases of paralysis agitans, perivascular sclerosis, ischemic sclerosis and rarefactions in the form of necrotic foci. Demange,[5] Leyden,[6] Eisenlohr,[7] Oppenheim,[8] Siemerling,[9] Sanders [10] and others reported cases of senile paraplegia and senile paralysis due to sclerotic changes, involving especially the perivascular white matter. We have observed similar cases. Although no cavitations of the cord were noted in the cases reported by the aforementioned authors, it is well to bear in mind that occasional cavitations may occur in areas of softening after absorption of degenerated products. At times these cavities, such as those in case 1, may become surrounded by a dense connective tissue wall. Sometimes such cavities in the cord traverse several segments of the cord and produce a clinical picture of syringomyelia. This occurred in the 2 cases which we report. Before necropsy the true nature of the condition was not suspected by most neurologists. Indeed, on clinical grounds the differentiation from ordinary syringomyelia cannot

4. Henneberg, R.: Die Myelitis und die myelitischen Strangerkrankungen, in Lewandowsky, M.: Handbuch der Neurologie, Berlin, Julius Springer, 1918, vol. 2, p. 695.

5. Demange, E.: Contribution à l'étude des scleroses médullaires d'origine vasculaire, Rev. de méd. **4**:754, 1884; Contributions à l'étude des lesions scléreuses des vaisseaux spinaux, ibid. **5**:1, 1885.

6. Leyden, E.: Ueber chronische Myelitis und die Systemerkrankungen im Rückenmark, Ztschr. f. klin. Med. **21**:1, 1892.

7. Eisenlohr, C.: Akute Myelitis dorsalis, Virchows Arch. f. path. Anat. **73**:82, 1878.

8. Oppenheim, H.: Textbook of Nervous Diseases, translated by A. Bruce, New York, G. E. Stechert & Co., 1911, vol. 1 (*a*) p. 331; (*b*) p. 304.

9. Siemerling, cited by Oppenheim.[8a]

10. Sanders, cited by Oppenheim.[8a]

be made. We would point out that in case 1 the brain also showed cyst formation. Cavitation in the brain due to atherosclerosis is relatively common as compared with the rarity of such a process in the spinal cord. We believe that atherosclerotic myelopathic syrinx is rare because the collateral circulation in the cord supplied by the coronal vessels usually suffices to prevent its development.

Histopathologically, the pronounced atherosclerosis of the intraspinal vessels and the absence of a glial wall and ependymal lining throughout the cavity (except where a communication was made with the central canal) conclusively prove that these cavities were not those of true syringomyelia. Furthermore, in case 1 a dense connective (not glial) tissue surrounded the cavity.

In this connection, we would emphasize that Foix and Alajouanine [2] and others reported cavity formation in association with atherosclerotic vessels in some instances of "subacute necrotic myelitis." It is our opinion that in some of these cases the condition should be designated as atherosclerotic myelopathy with syrinx formation and not as true "subacute necrotic myelitis."

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# DIFFUSE LEUKOENCEPHALOPATHY WITHOUT SCLEROSIS

## CLINICOPATHOLOGIC STUDY OF A NEW FORM, WITH COMMENT ON VARIOUS TYPES OF SO-CALLED DIFFUSE SCLEROSIS AND SCHILDER'S DISEASE

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Schilder's disease and diffuse sclerosis are terms which have frequently been used in the neurologic and pediatric literature to designate a condition characterized pathologically by diffuse and symmetric degeneration of the white substance of the brain. The disease usually occurs in children, but it may also appear in adults, the patients showing signs of disease of the brain, such as muscular hypertonicity, spastic paralysis, tonic and epileptic fits, choreoathetoid movements and mental deterioration. The onset of the disorder is usually slow, and the course is variable but always progressive, leading to a fatal termination.

The terms Schilder's disease and diffuse sclerosis are popular among certain neuropathologists and neurologists. Many have not liked the former designation because Schilder, in describing his case, used the term "encephalitis periaxialis diffusa." In the majority of cases, however, signs of inflammation are not shown, and the disease is axial, as well as periaxial, since axis-cylinders, as well as myelin sheaths, are destroyed.

Since the degeneration of the white substance is accompanied by proliferative changes on the part of the astroglia, the disease in the majority of cases has come to be called "diffuse sclerosis." This term has been accepted by many authors despite the fact that there are cases that do not come under this heading at all in which the disorder is characterized by a rather diffuse, but not always symmetric, proliferation of the glia in the centrum semiovale, resulting from such factors as localized inflammation, anoxia and birth trauma. In some instances the degeneration of the white matter is not combined with proliferative changes on the part of the astroglia, and therefore the term "diffuse leukoencephalopathy" has been used. This term seems appropriate, for it does not assume anything as to the nature or the final outcome of the process. The characteristics of so-called diffuse sclerosis are derived from the gross appearance of the brain and from what is seen in preparations stained to show myelin sheaths. The common feature is the more or less symmetric demyelination of the centrum semiovale in both hemispheres and usual relative sparing of the U fibers. When the U fibers are also degenerated, the degenerative process at these points is never as intense as in the centrum semiovale. Since this characteristic is noted in almost all cases of diffuse sclerosis, it seems to be independent of the actual demyelinating process and may be due to a specific resistance of the U fibers themselves to any number of pathogenic agents.

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From the Illinois Neuropsychiatric Institute and the Department of Neurology and Neurological Surgery, University of Illinois College of Medicine, Chicago, and the Lincoln State School and Colony, Lincoln, Ill.

We describe here 2 cases of a seemingly new or rare disease with distinctive clinical features which occurred in siblings; in the case in which we had the opportunity to make a pathologic examination the changes in the brain were unusual.

We are averse to the coining of new names, which often confuse, rather than clarify, the subject; hence we shall use the term "diffuse leukoencephalopathy," adding the qualification "without sclerosis," for the absence of sclerosis is a distinctive pathologic feature.

## REPORT OF CASES

The 2 patients described here were siblings, a brother and a sister, and their parents were second cousins. A carefully obtained history revealed no significant neurologic disorder in the antecedents. A third sibling, a younger sister of the patients, was examined in 1941, at the age of 7 years, and no evidence of neurologic disorder was present.

CASE 1.—*Personal History.*—L. A., a white youth, first in the order of birth, was born in 1925 at full term and appeared normal. Delivery was normal. At the age of 1 year it was noted that his head was becoming disproportionately large for the rest of his body. He began to walk at the age of 18 months, but although he was able to get about, he stumbled easily, could not walk fast or run and had a scissors gait. From the age of 4 years his gait became progressively worse until, at the age of 7 years, he was wholly unable to walk and could only crawl about. He had never been able to use his upper extremities normally. His movements were always jerky, and this disturbance became rapidly worse at the age of 9 years.

Examination at the University Hospitals,[1] Iowa City, in 1934 revealed that he was well developed and well nourished. He was unable to sit up without support but slumped in his chair. The pupils were equal and reacted sluggishly to light. The upper extremities were somewhat rigid but showed little ataxia, the incoordination being greater on the left side than on the right, and the biceps reflex was obtainable. The lower extremities showed some resistance in the adductor muscles; the patellar reflex was brisk on the right side and of the "hang-up," or suspended, type (as in chorea) on the left side. Neither the Babinski sign nor ankle clonus was obtainable. With support the boy stood on his toes; he walked with a typical steppage gait, the legs occasionally assuming a scissors position. His intelligence quotient was 50 to 56. At this time a clinical diagnosis of spastic paralysis with mild hydrocephalus was made. From 1934 until 1941 he was cared for by his parents. In 1938, at the age of 13 years, he had a severe epileptiform seizure, his first, after which speech was almost completely lost, but he seemingly understood everything spoken to him. After this episode he continued to have seizures at irregular intervals. He was admitted to the Lincoln State School and Colony in November 1941, together with his sister, B. A., our second patient.

*Physical Examination.*—The boy appeared to be normally developed for his age and was fairly well nourished. Examination of the heart and lungs revealed nothing significant. He was completely helpless and crippled and unable to speak, but he could see and hear and seemed to understand what was said to him. The head was hydrocephalic; the forehead was bulging, and the cephalic circumference was 57 cm. There were continuous athetotic movements, affecting especially the muscles of the face, the tongue and the upper extremities. These were slow and twisting, and sometimes the entire body was involved, much as in torsion spasm. He had an outstanding tendency to have forced, involuntary laughter, and frequently, while responding to a caress with a smile, he would suddenly burst into a roaring guffaw, which was accompanied by forced inspirations. The lower extremities were spastic and were kept in a scissors position; they were the seat of much less motor restlessness than was the face or the upper extremities. The joints of the wrists and ankles were stiff, and the feet were in an equinovarus position. The pupils reacted to light and in convergence; extraocular movements were good; the optic fundi were normal, and no Kayser-Fleischer ring was observed. There was generalized hyperreflexia, with a positive Babinski sign bilaterally. The abdominal reflexes were not obtainable. The extremities at all times were rigid and spastic. The patient continued to have severe epileptiform seizures, and in March 1942 bronchopneumonia developed, of which he died, at the age of 17 years and 1 month. The postmortem examination in this case will be reported later.

CASE 2.—*Personal History.*—B. A., a white girl, second in order of birth and the sister of L. A., was born at full term in April 1929. Labor was precipitate, lasting only one hour, and the weight at birth was 6¾ pounds (3,062 Gm.). The patient did not try to walk until

1. The Hospital of Orthopedic Surgery, State University of Iowa College of Medicine, sent us copies of the case histories.

she was 16 months of age, but even before that time the parents noticed that there was marked adduction of the thighs and that her head was larger than that of other children of her age. When she was 2 years of age her head measured 58 cm. She never had normal use of her arms but could move the left one better than the right. Speech and mental condition seemed to be normal up to the age of 4 years, when she had two rather severe convulsions, after which she spoke only in monosyllables and no longer formed sentences. Speech and gait became progressively worse until, at the age of 5 years, she could no longer walk or talk. At that time, in 1934, when she was examined at the University Hospital, Iowa City, she appeared frail and underdeveloped. She could sit up, but her head dropped forward. The pupils were round and equal, reacting to light and in convergence. Her head was hydrocephalic. The upper extremities were reported to be rather spastic at times, and the lower extremities were said to show considerable spasticity of the adductor muscles and to be in a marked scissors position. Both feet were in an equinovarus position, and the presence of a Babinski sign was suggested on the right side. She was admitted to the Lincoln State School and Colony in November 1941, at the age of 12 years.

*Physical Signs.*—The patient was poorly nourished, and her head was hydrocephalic, being 58 cm. in circumference. She could see and hear but could not speak. She seemingly understood what was said to her, but not as well as her brother (case 1). In contrast to her brother, she showed no involuntary movements. Her face was immobile and masklike; all four extremities were spastic, and the deep tendon reflexes were exaggerated. During her stay in the Lincoln State School she continued to have epileptiform seizures. She began to gain in weight, but gastrointestinal symptoms developed, and she died in a state of extreme emaciation in August 1942, at the age of 13½ years. Permission for postmortem examination was not given.

### NECROPSY (CASE 1)

*Macroscopic Observations.*—Except for diffuse bronchopneumonic changes in both lungs, the essential pathologic process was restricted to the brain. The bones of the skull were rather hard and were about 0.75 cm. thick. The dura mater was not adherent to the skull. The brain weighed 1,500 Gm. The leptomeninges were thin and transparent. The frontal gyri were flattened, and both frontal lobes were soft and ballotable. Coronal section through the frontal lobes revealed that the white matter in the centrum semiovale was a grayish white, semiliquid mass, which drained out, an apparently normal cortex being left. The cavity was lined on the inside with a narrow band of white matter (fig. 1). Fine white strands and lamellas were sometimes left in places from which the fluid had drained out. Evidently, they represented small blood vessels and pial membrane. In areas where the process seemed to be less advanced the white matter was changed into a gelatinous, semiopaque, soft substance. The lateral ventricles were only slightly enlarged. Coronal sections farther back showed that the white substance was similarly affected, but not to so pronounced a degree, and in the occipital lobes the subcortical white substance in places appeared normal on gross inspection. The basal ganglia were grossly normal, as were the corpus callosum and the internal capsule. The midbrain and the hindbrain showed no gross changes. Some of the semiliquid mass that escaped on section of the brain was stained with sudan III, and the remainder of the brain was fixed in a 4 per cent concentration of solution of formaldehyde U. S. P. and in 95 per cent alcohol.

*Microscopic Observations.*—Examination of the semiliquid substance that ran out of the centrum semiovale, smears of which were stained with sudan III, showed amorphous sudanophilic material but no compound granular corpuscle cells (gitter cells).

Blocks of tissue from different portions of the brain were embedded in pyroxylin and in paraffin for detailed microscopic study. Sections from these blocks were subjected to a variety of stains and impregnation technic. Frozen sections were stained with sudan III.

In preparations stained for myelin sheaths the areas which were described as soft or semiliquid in the gross specimen were seen to be demyelinated. These alterations were most pronounced in the frontal and the parietal lobe and were present to a far slighter degree in the temporal and the occipital lobe. In a coronal section through the splenium of the corpus callosum (fig. 1 *B*) the diffuse demyelination in the centrum semiovale and in the subcortical white substance of the superior frontoparietal convolutions stood out in marked contrast to the normal-appearing and heavily myelinated splenium of the corpus callosum and the internal and external sagittal strata. The contrast between the heavily involved superior frontoparietal convolutions and the unaffected or partially affected convolutions of the temporal lobe was also striking. From the study of many sections, it appeared that the disorder had started in the centrum semiovale and spread into the adjacent subcortical white substance, the U, or arcuate, fibers, which connect one convolution with its neighbor, being affected last. Whereas

the U fibers were spared in many places, in other regions they, too, were destroyed. The intracortical fibers were only slightly affected, and the dense fiber tracts, such as the corpus callosum, the fornix and the uncinate fasciculus, the optic nerves and optic chiasm and the optic radiations were not involved.

In frozen sections stained for fat with sudan III and other specific stains the changes were more striking. Despite the extreme "softening" of the tissues, no fat-filled compound granular corpuscles (gitter cells) could be found. These were sought for not only in the centrum semiovale, where the process was of many years' standing, but in the foci which apparently had been only recently affected. Sudanophilic material was present in the tissues but was amorphous and granular. The endothelial cells lining the capillaries in the cortex, however, did show pseudophagocytic activity, as evidenced by the crowding of their cytoplasm with sudanophilic material (fig. 2 *A*). In sections prepared with the Pal-Weigert stain, sudan III and Mallory's phosphotungstic acid hematoxylin the fragmentation and varicose swelling of the myelin sheaths were striking (fig. 2 *B*). In sections prepared by the Cajal and Hortega methods neither the astroglia nor the oligodendroglia appeared to be proliferated. The number of astrocytes was not increased. In the gelatinous portions aforementioned, these

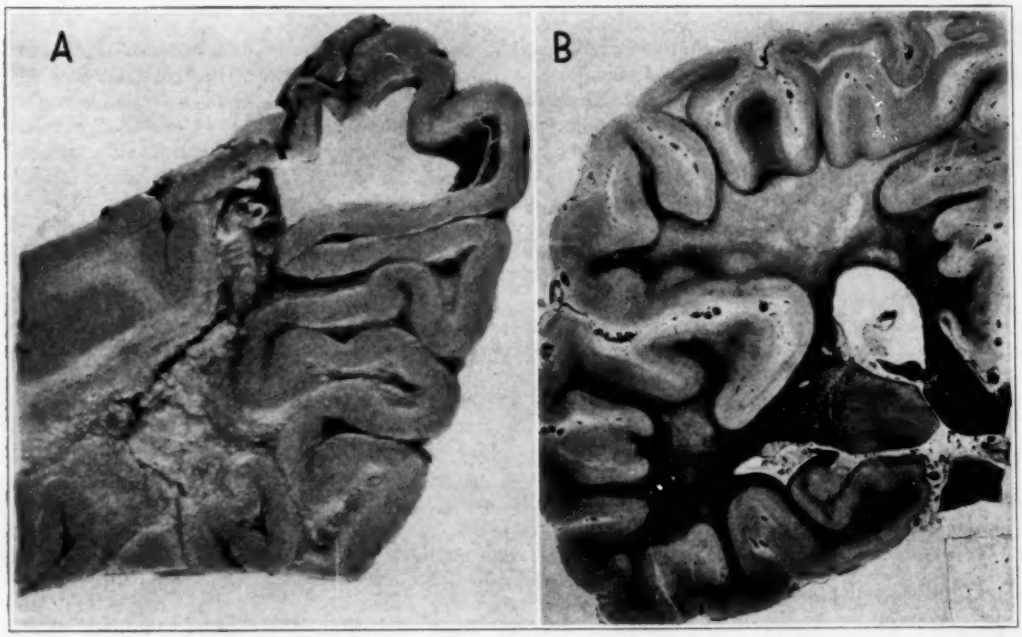


Fig. 1.—*A*, gross section of the brain through the frontal lobe, showing alteration in the texture of the subcortical white substance and centrum semiovale. *B*, coronal section through the left cerebral hemisphere at the level of the splenium of the corpus callosum, showing the diffuse demyelination of the white substance with sparing of the U fibers. Weigert-Pal stain.

elements stained poorly by the gold chloride–mercury bichloride method, and their bodies were slightly swollen. There was no specific relation of these elements to the degenerating myelin sheaths.

The absence of a mesenchymal or phagocytic reaction on the part of the histiocytic elements was paralleled by complete absence of evidence of proliferative activity on the part of other mesenchymal elements, such as the fibrocytes. Although the disorder was of about sixteen years' duration, silver nitrate–tannic acid preparations failed to show an increase in the perivascular reticulum (fig. 3 *A*). Suffice it to say that no evidence of an inflammatory reaction was noted, polymorphonuclear leukocytes, lymphocytes and plasma cells being absent.

Silver preparations for the demonstration of axis-cylinders in sections from the heavily demyelinated areas showed moderate diminution in the number of neurites. This alteration was not entirely an artefact caused by the fluid condition of the white substance, but it was to some extent. In better preserved areas the decrease in the number of axis-cylinders appeared to be slight. That there was some interruption of neurites in vivo was evidenced by the secondary degeneration in the corticospinal tracts in the medulla oblongata and the upper cervical segments of the spinal cord. The reactive deficiency on the part of the glia

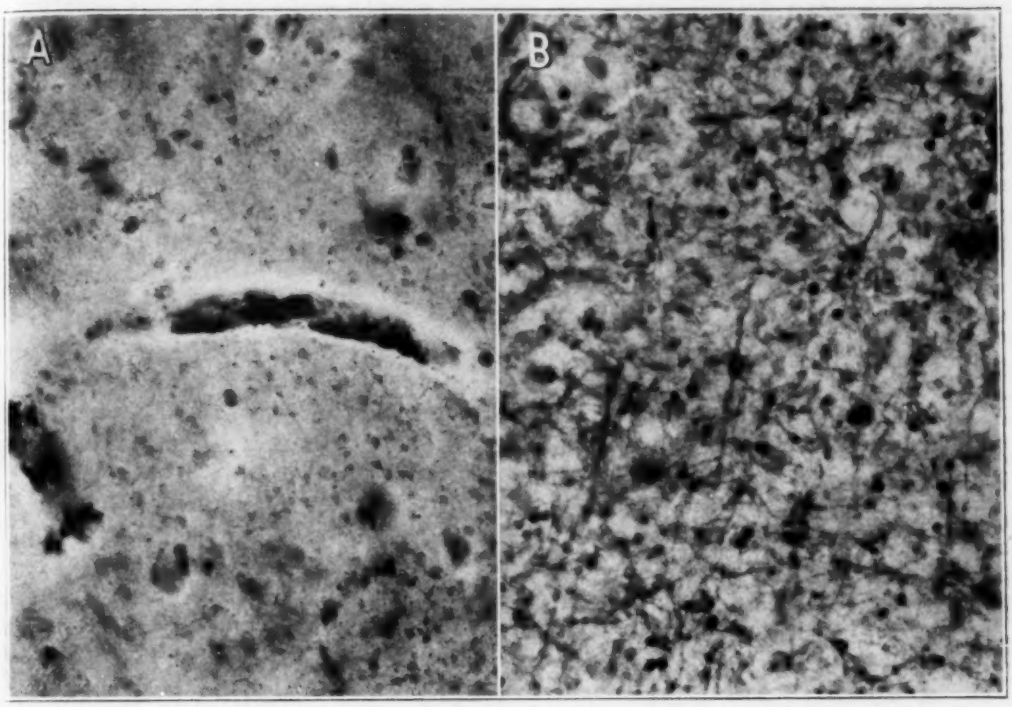


Fig. 2.—*A*, photomicrograph of a section through the cortex of the frontal lobe in an affected area, showing the cytoplasm of the endothelial cells filled with a fatty substance. Oil red O stain. *B*, photomicrograph of a section through the partially affected white substance, showing pyknotic glial nuclei, as well as swelling and fragmentation of the myelin sheaths. Mallory's phosphotungstic acid hematoxylin stain.

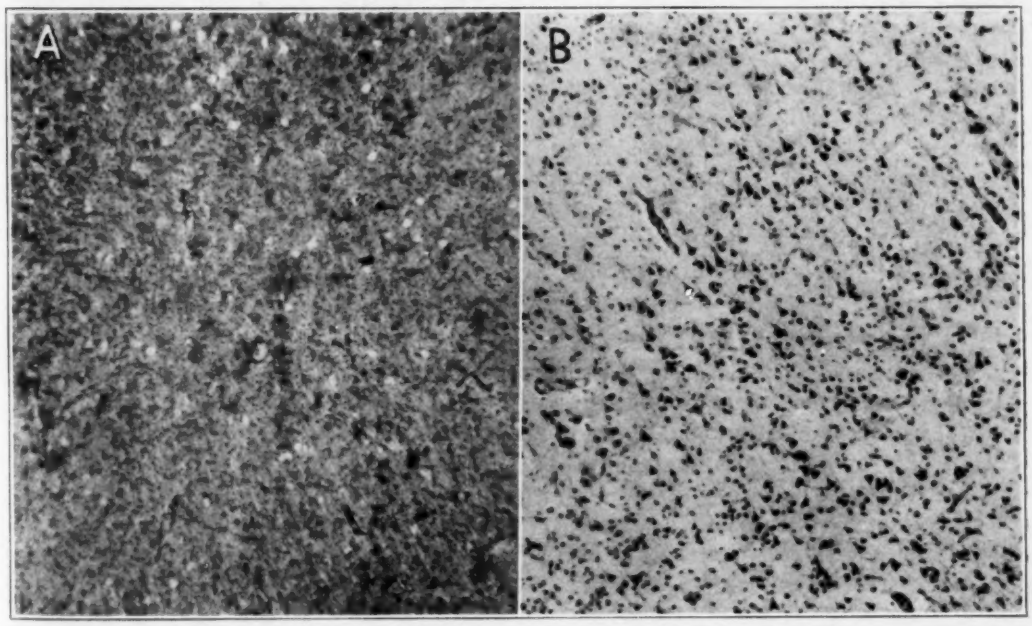


Fig. 3.—*A*, photomicrograph of a section through the affected white substance, showing absence of proliferation of reticulum. Silver–tannic acid stain. *B*, photomicrograph of a section through the cerebral cortex overlying an affected area, showing the relative preservation of the nerve cells except for atrophy of some of them. Cresyl violet stain.

and the mesenchyme-derived elements was restricted to the primary foci of degeneration, for in the areas of secondary degeneration in the pyramidal tracts normal reactive changes were seen.

The cerebral cortex overlying the diseased areas showed no notable pathologic changes. On the whole, it was exceedingly well preserved as compared with the subcortical white substance and the centrum semiovale (fig. 3*B*). In some fields occasional swollen nerve cells were seen, and in others pale areas contained ghostlike shadows of nerve cells. Many of the remaining ganglion cells were atrophic. Neither satellitosis nor neuronophagia was evident. In the affected areas the oligogliocytes showed pyknosis, their nuclei being small and hyperchromatic and their cytoplasm swollen and pale staining. We did not see the peculiar large glial nuclei which Jervis [2] described recently in the cortex in 2 cases of diffuse sclerosis.

## CLINICAL CONSIDERATIONS

*Summary of Cases.*—The 2 siblings described, children of parents who were second cousins, showed very early in life, probably soon after birth, a hydrocephalic-like enlargement of the head and signs of motor difficulty in the nature of jerky movements of the upper extremities and a scissors position of the lower extremities. Both started to walk later than normal, and the gait was always unstable. The older child had his first seizure at the age of 13 years, after which he apparently lost ability to speak. The younger child had her first convulsion at the age of 4 years, after which ability to speak became poor. Later her speech deteriorated until it was completely lost. Whereas the older sibling manifested spasticity until the age of 9 years, after which choreoathetoid and torsion movements developed, the younger sibling exhibited spasticity until the age of 12 years, when mask-like rigidity of the face was noted. Both siblings, although physically disabled and practically aphasic, maintained a rather high level of mentality until death. There can be hardly any doubt that the girl, on whom autopsy could not be performed, had the same disorder as her brother, the changes in whose brain have been described.

*Diagnosis.*—The condition of both children was diagnosed as diffuse sclerosis during life. From the clinical history it was apparent that both suffered from the same disorder, and since both parents were healthy, but were second cousins, the disorder was considered to be familial, with a recessive gene as the probable basis. Wilson's disease was ruled out by the absence of a Kayser-Fleischer ring and signs of hepatic damage. Against a diagnosis of hereditary ataxia were the extreme spasticity, the frequent convulsions and the absence of real ataxia or Friedreich's foot. The possibility of late infantile or juvenile amaurotic idiocy without amaurosis was considered, but against such a diagnosis was the maintenance of rather good mentality despite pronounced physical deterioration. A diagnosis of diffuse sclerosis seemed, therefore, the most probable.

## COMMENT

The cases which have been verified as instances of this disease by the presence of the paramount feature of the disorder, namely, progressive, diffuse, symmetric demyelination of the centrum semiovale and subjacent white substance, have been tentatively divided into several groups. Neubuerger [3] differentiated between a blastomatous, an inflammatory and a degenerative form of the disease, but, in our opinion, neither the blastomatous nor the primary inflammatory form should be designated as "diffuse sclerosis" or "diffuse leukoencephalopathy." If the spread of a tumor results in diffuse demyelination, the tumor represents the chief pathologic

2. Jervis, G. A.: Early Infantile "Diffuse Sclerosis" of Brain (Krabbe's Type): Report of Two Cases with Review of Literature, Am. J. Dis. Child. **64**:1055 (Dec.) 1942.

3. Neubuerger, K.: Histologisches zur Frage der diffusen Hirnsklerose. Ztschr. f. d. ges. Neurol. u. Psychiat. **73**:336, 1921.

process and should determine the name of the pathologic picture. The same is true of an inflammatory process. Evidently, the classification of such different processes under a common head is a relic of the days when the staining of myelin sheaths was the standard method of study in neuropathology. Such a means, however, is not justified today, when there are available methods which allow a finer analysis of the pathologic process. On the other hand, the cases belonging to the so-called degenerative type of diffuse sclerosis have many features in common, namely, absence of primary inflammation and evidence of a hereditary factor. We think that, for the time being, the terms "diffuse sclerosis" and "diffuse leukoencephalopathy" should be restricted to cases of this type, although they may not represent a specific entity.

The cases belonging to this category have been classified according to the period of onset, as the infantile, the juvenile and the late type; according to the course, as the acute, the subacute and the chronic form, and according to the names of the investigators, as the Krabbe,[4] the van Bogaert–Scholz [5] and the Merzbacher–Pelizaeus [6] type. Bielschowsky,[7] in particular, had the tendency to correlate the age of onset and the course, thus identifying the acute with the infantile, the subacute with the juvenile and the chronic with the late form, the last type being represented by the Merzbacher-Pelizaeus cases, despite the fact that the picture of the brain, as seen in sections stained for myelin sheaths, was rather different from that seen in typical instances of diffuse sclerosis. Wilson,[8] however, pointed out that this simplification was unjustified, for a form of early onset may run a chronic course and a form starting later in life may run an acute course. In general, however, and in spite of many exceptions, an early onset seems to be associated with an acute course, as described by Krabbe.

The cases of the 2 children reported here are unusual in their clinical aspect inasmuch as, despite a very early onset, the disease ran an extremely chronic course. Furthermore, in both cases enlargement of the head became apparent early and later remained stationary. This enlargement was sufficiently great to suggest the diagnosis of hydrocephalus. In both cases acute and extreme deterioration in speech began with the onset of epileptiform seizures, a phenomenon suggesting an acute progression of the disorder in episodes. In neither case was there evidence of visual disturbance, which is usually described as an early sign associated with diffuse demyelinating processes.

Although both siblings manifested typical spasticity in life, the boy later showed choreoathetoid movements and torsion spasm, while the girl exhibited masklike rigidity of the face and died, it is likely, before she reached the stage at which she would have presented more pronounced extrapyramidal signs. To our knowledge, no case of diffuse sclerosis with enlargement of the head has ever been described, and in this respect our cases seem to be unique.

Our cases are remarkable, furthermore, because of the duration of the disease. That was especially true in the first case, in which the illness was of sixteen years' duration. Cases of diffuse sclerosis with an early onset and a rather protracted course have been described, however. Wilson reported 8 cases from the

4. Krabbe, K.: A New Familial Infantile Form of Diffuse Brain Sclerosis, Brain **39**: 74, 1916.

5. (*a*) van Bogaert, L., and Scholz, W.: Klinischer, genealogischer und pathologisch-anatomischer Beitrag zur Kenntnis der familiären diffusen Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **141**:510, 1932. (*b*) Scholz, W.: Klinische, pathologisch-anatomische und erbbiologische Untersuchungen bei familiärer diffuser Hirnsclerose im Kindesalter, ibid. **99**:651, 1925.

6. Merzbacher, L.: Eine eigenartige familiärhereditäre Erkrankungsform, Ztschr. f. d. ges. Neurol. u. Psychiat. **3**:1, 1910.

7. Bielschowsky, F.: Die Bedeutung des Infektes für die diffuse Sklerose, J. f. Psychol. u. Neurol. **33**:12, 1927.

8. Wilson, S. A. K.: Neurology, Baltimore, Williams & Wilkins Company, 1940, vol. 2.

literature in which the illness lasted ten or more years. One member of the family described by him, and also by Symonds,[9] died after an illness of fifteen years, and another member of this family was still alive eighteen years after the first symptoms had appeared. Recently, Junker [10] reported a case somewhat similar to our cases, in which a girl fell ill at the age of 3 years. Her first symptom was difficulty in walking, and this progressed slowly until the age of 16 years, when mental deterioration set in. She began to have convulsions at 19 years of age, and these continued to occur until her death, at the age of 22 years. The clinical picture in its final stages was extreme dementia with spasticity. Vision was not affected. Although the onset in Junker's case was somewhat later than that in our cases, the clinical course and some of the pathologic characteristics of the disease, to be described later, closely paralleled the features in our cases.

Changes in the major symptoms of heredodegenerative disease do occur. Thus, in families with Huntington's chorea some of the affected members at an early age may show an akinetic syndrome. One of us (H. J.) described a family with hereditary ataxia in which the ataxia finally changed into a torsion syndrome, this change probably coinciding with the progression of the pathologic process.

It appears that diffuse leukoencephalopathy has familial features, as does hereditary cerebellar ataxia, and that each affected family has "its own disease." There may even be differences between 2 cases in the same family, or at least in cases occurring in different generations. It is interesting to note that in the families described by Scholz,[5b] Bielschowsky and Henneberg [11] and Curtius [12] some ascendants of the members afflicted with diffuse sclerosis suffered from familial spastic spinal paralysis. Mackay [13] described 3 cases in which the clinical course was characterized by microcephaly, idiocy, convulsions and spastic paralysis. In his series the disorder was nonfamilial; in 1 case the pathologic process was nonprogressive and in another the glial reaction was minimal.

## PATHOLOGIC CONSIDERATIONS

Even more unusual than the atypical clinical course in our cases was the pathologic picture. The brain in our case in which autopsy was performed showed no signs of sclerosis on either gross or microscopic examination, the white substance, on the contrary, being semiliquid. In this respect our case resembles the case of Junker previously mentioned, in which the clinical course was also protracted. The brain in our case weighed 1,390 Gm., and sections through the hemispheres revealed semiliquid portions. Microscopic examination, however, revealed gitter cells, and in some places there was notable proliferation of the fibrillar glia cells, which formed a membrane about the liquefied portions.

Such liquefaction of the centrum semiovale has been described in certain cases of family amaurotic idiocy (Bielschowsky [14]; Ostertag [15]) but not, to our knowledge,

9. Symonds, C. P.: A Contribution to the Clinical Study of Schilder's Encephalitis, Brain **51**:24, 1928.

10. Junker, W.: Beitrag zur Kenntnis der diffusen Sklerose, Arch. f. Psychiat. **111**:115, 1940.

11. Bielschowsky, M., and Henneberg, R.: Ueber familiäre diffuse Sklerose, J. f. Psychol. u. Neurol. **36**:131, 1928.

12. Curtius, F.: Familiäre diffuse Sklerose und familiäre spastische Spinalparalyse in einer Sippe, Ztschr. f. d. ges. Neurol. u. Psychiat. **126**:209, 1930.

13. Mackay, R. P.: Congenital Demyelinating Encephalopathy, Arch. Neurol. & Psychiat. **43**:111 (Jan.) 1940.

14. Bielschowsky, M.: Zur Histopathologie und Pathologie der amaurotischen Idiotie, J. f. Psychol. u. Neurol. **26**:123, 1920.

15. Ostertag, B.: Entwicklungsstörungen des Gehirns und zur Histologie und Pathogenese besonders der degenerativen Markerkrankung bei amaurotischer Idiotie, Arch. f. Psychiat. **75**:355, 1925.

in cases of so-called diffuse sclerosis, except in the aforementioned case reported by Junker.[10] In all these cases the liquefaction of the white matter was not accompanied by enlargement of the head. In our cases the quantity of semifluid substance formed from the centrum semiovale was evidently increased to such a degree that the brain and the skull became greatly distended.

Bielschowsky, as well as Ostertag, explained the softening of the white matter by a supposedly increased water-binding potency of the decomposed myelin. As for our cases, there must have been additional disturbance. A surplus of fluid must have been retained in the destroyed portions of the centrum semiovale and have produced a pressure high enough to distend it against the normal intracranial pressure. The tissues seem to have been unable to filter off the fluid into the normal channels—the subarachnoid spaces or the ventricles. A disturbance in the osmotic pressure between the blood and the tissue fluids, on the one side, and the decomposed myelin, on the other, may have played a role in the development of this pseudohydrocephaly. We are, however, somewhat reluctant to offer a simple chemicophysical explanation for a phenomenon occurring in living substance.

In our case the degeneration was restricted to the subcortical white substance and the centrum semiovale, but in other instances of diffuse sclerosis the corpus callosum, the optic chiasm, the anterior commissure and other white masses have been involved. In this respect the disorder resembles Marciafava's disease, or primary degeneration of the corpus callosum, in which the essential pathologic process is in the callosal body but in which the anterior commissure, the optic chiasm, the centrum semiovale and other white masses are sometimes involved as well.

The complete absence of any reaction to the disintegration of myelin sheaths is the most significant histologic feature in our case. There were neither gitter cells nor any evidence of proliferation of the macroglia. Neither was there any reaction of the mesenchymal tissue. It is worth noting that this lack of normal reactive response was restricted to the centrum semiovale. Reactive processes in other regions of the brain were normal, as shown in the areas of secondary degeneration. This indicates a disturbance in the centrum semiovale rather than in the glia and the mesenchyma in general, and the case can be considered as an example of pathoclisis, in accordance with the concept expressed by C. and O. Vogt[16] of a specific endogenous morbidity of certain regions of the nervous system. The absence of any reaction to long-standing degeneration of an essential parenchymatous element seems to have hardly any analogy in the brain or any other organ.

## GENERAL CONSIDERATIONS

It is rather well established that the cases of so-called degenerative diffuse sclerosis represent a type of heredodegeneration of the nervous system. Indeed, many "isolated" cases have been reported in the literature in which no proof of a familial or hereditary taint could be found. The number of cases in which heredity is an etiologic factor is increasing, however, and is now large enough to permit the conclusion that the condition should be classified as a form of heredodegeneration. Our cases are good examples of this hereditary factor, for the occurrence of the disease in 2 siblings, offspring of parents who were blood relatives, is sufficient evidence of the action of a recessive gene.

There are numerous theories as to the pathologic classification of the underlying process of the demyelination. As was pointed out before, the picture in

16. Vogt, C., and Vogt, O.: Erkrankungen der Grosshirnrinde im Lichte der Pathoklise und Pathoarchitektonik, J. f. Psychol. u. Neurol. **28**:1, 1922.

preparations stained to show myelin sheaths, although pathognomonic to a certain degree, does not reveal the exact nature of the pathologic process. The degenerative form of diffuse sclerosis may not even be a specific morbid entity and may later have to be subdivided. The many subgroups may represent only variations of the same process, that is, differences in the degree and the speed of reaction only. It is hardly possible to decide the question as long as no more is known about the early stages of this process. The fact remains that one may find in the group of the degenerative form cases with abundant glial reaction, cases with production of peculiar abnormal metabolic products (Kaltenbach [17]) and, finally, cases, like ours, with no reaction at all.

The basic defect behind the demyelination has been stated by most authors to be a disorder of the glia, as this element is regarded as instrumental in myelogenesis, as well as in nutrition and regeneration of the myelin sheaths. Collier and Greenfield [18] suggested that primary involvement of the glia is resposible for the disease of the myelin. Scholz discussed the possibility that a hereditary anomaly of the glia influences the metabolism of myelin. The oligodendroglia, in particular, has been accused by many investigators, among whom have been Levaditi [19] and Greenfield.[20]

As for our case, the insufficiency of the glia is evident from the histologic observations. This insufficiency is probably a hereditary defect and is, as such, hardly accessible to further analysis.

SUMMARY

Two cases of diffuse leukoencephalopathy (diffuse sclerosis) occurring in siblings are described. Since the parents of the patients were blood relatives, it is likely that the disease was transmitted by a recessive gene. The remarkable clinical features in these cases were the long duration of the disease, which started in early life, and the striking enlargement of the head, which was so marked as to suggest hydrocephalus.

The brain of the sibling studied post mortem showed a peculiar liquefaction of the centrum semiovale of both hemispheres. The remarkable microscopic feature was the complete absence of reaction on the part of the glia and the mesenchymal tissues to the presence of the degenerated myelin.

Degenerative diffuse sclerosis is generally a familial or hereditary disorder, despite the occurrence of sporadic cases. It should be distinguished from the so-called blastomatous, primary inflammatory, anoxic and traumatic varieties of diffuse sclerosis. In our case the term "diffuse leukoencephalopathy" seems more appropriate than "diffuse sclerosis," since there was no sclerosis. Whether the various clinical morphologic types of degenerative diffuse sclerosis represent different morbid entities or are only variations of a single basic process remains open for discussion.

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17. Kaltenbach, H.: Ueber einen eigenartigen Markprozess mit metachromatischen Abbauprodukten bei einen paralyseähnlichen Krankheitsbild, Ztschr. f. d. ges. Neurol. u. Psychiat. **75**:138, 1922.

18. Collier, J., and Greenfield, J. G.: The Encephalitis Periaxialis of Schilder, Brain **47**: 489, 1924.

19. Levaditi, C.: Les ultravirus provocateurs des ectodermoses neurotropes, Ann. Inst. Pasteur **45**:673, 1930.

20. Greenfield, J. G.: A Form of Progressive Cerebral Sclerosis in Infants Associated with Primary Degeneration of the Interfascicular Glia, J. Neurol. & Psychopath. **13**:289. 1933.

# Case Reports

## OPHTHALMOPLEGIA INTERNUCLEARIS

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Ophthalmoplegia internuclearis, as described by Lhermitte, is a rare neurologic disorder characterized by dissociation of lateral conjugate movements of the eyes. Instead of moving parallel or nearly parallel with each other, the two eyes move separately. For example, on the patient's looking to the right the right lateral rectus muscle and the left medial rectus muscle do not contract to an equal extent, the lack of coordination giving rise to dissociated movement and double vision. According to Bing and Haymaker,[1] the defect is in the lateral plane, and convergence is not affected.


*A*, paralysis of the left lateral rectus muscle on the patient's attempting to look to the left. *B*, normal convergence on the patient's looking downward. (Photographs by the United States Army Signal Corps.)

In the case to be reported, there was paralysis of conjugate upward movement as well as of lateral movement. Convergence was the only associated movement left the patient.

### REPORT OF A CASE

R. J., an infantryman aged 30, white, was admitted to the Station Hospital, Camp Carson, Colo., on April 5, 1943, with the complaint of extreme double vision.

*Present Illness.*—The patient had been well until the day before admission, when he had contracted a cold, coincident with several days of firing on the rifle range. At this time there developed diplopia so severe that he had to be led to the hospital. The nasopharyngitis soon cleared up, but the diplopia persisted.

*History.*—The patient had been a farmer up to the time of his induction, on Jan. 26, 1943. He had never smoked or drunk alcoholic beverages. He had finished the tenth grade and had been married for five years.

Read before the Colorado Neurologic Society, May 22, 1943.

From the Neuropsychiatric Service, Station Hospital, Camp Carson, Colo.

1. Bing, R., and Haymaker, W.: Textbook of Nervous Diseases, St. Louis, C. V. Mosby Company, 1939, p. 70.

He had always had a tendency to double vision, especially when looking into the distance. He could, however, always "make his eyes track" by voluntary effort except once, at the age of about 15 years, when his "eyes crossed" for two days. At this time he had had an attack of "flu." Glasses had been worn for ten years for "far sightedness," with some slight relief.

*Examination.*—Physical examination, including a complete neurologic study, revealed nothing abnormal except for the eyes. Vision was 20/200 in both eyes without correction and 20/40 in both eyes with correction for hyperopia. The eyes were otherwise normal except for a peculiar type of extraocular paralysis.

At rest both eyes looked straight ahead. On the patient's looking to either side the lateral recti muscles failed to contract (fig., *A*), and on his attempting to look upward both eyes remained fixed straight ahead or paradoxically turned downward and inward in convergence. This paradoxic convergence was also seen occasionally when the patient tried especially hard to look to either side. Covering of one eye did not alter the paralysis.

The severity of the paralysis fluctuated from day to day. On some days, when the patient was rested and before he had been tested too much, the first few efforts at lateral conjugate movements were successful. Fatigue soon eliminated the lateral movement of each eye and later the upward movement of both eyes, only the downward and inward movement of convergence being left (fig., *B*). At the time of his discharge from the Army, a month later, almost normal conjugate movement had returned except on his becoming fatigued. The responses to the caloric and turning tests were normal.

*Differential Diagnosis.*—Myasthenia gravis was ruled out by the lifelong history and the absence of any other evidence of muscular weakness, especially ptosis. Prostigmine had no effect on the extraocular paralysis.

Psychoneurosis was ruled out by the fluctuating nature of the paralysis and its relation to fatigue rather than to suggestion. It was also felt that the bizarre movements of the eyes could not possibly have been functional, especially since they could be explained by a specific organic disease.

*Diagnosis.*—The diagnosis was ophthalmoplegia with dissociation of all conjugate movements of the eyes except convergence.

## COMMENT

The lesion in this case was undoubtedly a congenital weakness of that part of the medial longitudinal fasciculus which has to do with coordination of the nuclei of the third, fourth and sixth cranial nerves into associated conjugate movements of the eyes. Usually the patient was able to overcome this weakness, but during the two periods of stress, one at the age of 15 years, during an attack of "flu," and the other at the age of 30, while he was in the Army, he was unable to "make his eyes track." Fatigue seemed to be the largest single factor in aggravating the ocular condition.

The survival of convergence when all other associated movements of the eyes were lost confirms the existence of the nucleus of Perlia. This part of the nucleus of the third nerve subserves the function of convergence, which is phylogenetically older than the functions of binocular vision. The phylogenetically older vestibulo-oculomotor connections of the medial longitudinal fasciculus were also uninvolved. The defect in this case might well have been an atavistic degenerative process affecting the biologically recently acquired neural mechanism of binocular vision. The patient's ocular movements at their worst reminded one of the movements of the eyes of fish as viewed through the glass plate at the aquarium.

The treatment of this disorder consists in all possible improvement of the general vitality, rest, avoidance of fatigue and correction of refractive errors. Any form of exercise of the eyes is contraindicated, as it serves only to fatigue the neural mechanisms involved.

## SUMMARY

A case of ophthalmoplegia characterized by dissociation of all conjugate movements of the eyes except convergence is presented. In cases of this disorder previously described the dissociated movements were limited to the lateral plane.

The lesion was undoubtedly a congenital weakness of the fibers of the medial longitudinal fasciculus coordinating the nuclei of the third, fourth and sixth cranial nerves into the function of binocular vision. The phylogenetically older functions of convergence and the vestibulo-oculomotor connections were not affected.

# Clinical, Technical and Occasional Notes

## VENTRICULAR DRAINAGE AS A VALUABLE PROCEDURE IN NEUROSURGERY

### Report of a Satisfactory Method

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For many years neurosurgeons have resorted to ventricular drainage before, as well as after, operation in the surgical management of tumors of the brain. The methods varied, but drainage was usually executed by means of repeated ventricular taps through a burr opening into either of the lateral ventricles. The change in pressure necessarily was relatively rapid, and the accumulation of fluid recurred, so that in four to six hours the procedure had to be repeated, especially after operation. Even so, surgeons found the employment of drainage to be of distinct advantage in combating the increased intracranial pressure. Continuous ventricular drainage during the period when the intracranial pressure is at its height is, of course, highly desirable. In surgical procedures on cerebral tumors, for many reasons craniotomy should immediately follow the ventriculographic examination. A patient with a large cerebral tumor, resulting in greatly increased intracranial pressure, may for a few minutes, or even hours, be aided materially by drainage of the ventricular system. However, with partial obstruction to the system, the accumulation of fluid and lack of absorption of air or oxygen after the ventriculographic study has been carried out may well cause alarming symptoms in several hours. Also, if at the time of craniotomy the tumor is not removed, postoperative edema may prove fatal. Ventricular drainage in cases of internal hydrocephalus resulting from a subtentorial tumor is of value in an attempt at improvement of the patient's condition before a radical procedure is performed. This preliminary drainage, of course, is used only with patients who are dehydrated from vomiting and are in serious condition at the time of entrance to the hospital.

Since 1940, in all cases in this clinic in which a tumor of the brain was suspected, my associates and I have carried out a routine in performing the ventriculographic procedure and have found it to be of great help in trying situations.

It has been the experience of most neurosurgeons that even though the neurologic examination seemed to give definite information as to the exact location of the neoplasm, the bone flap was inaccurately placed and that if it had been placed slightly more anteriorly or posteriorly much time would have been saved and a more neatly executed operation would have been possible. For that reason, ventriculograms have been made in most of our cases.

#### METHOD

Ventriculographic studies are carried out in the usual manner by means of a burr opening 3.5 cm. to each side of the midline in the parieto-occipital region. The dura is opened and an avascular portion of the cortex exposed; the arachnoid is punctured with a sharp-pointed knife, and a ventricular needle is inserted into each ventricle. After the fluid has been allowed to escape and has been replaced by air, a no. 8 soft rubber catheter is inserted into the ventricle containing the most fluid, which is usually opposite the side of the tumor, or if the ventricles seem to be of equal size, the catheter is inserted into the right lateral ventricle. It can be inserted readily and will follow the track that has been made by the ventricular needle. The scalp is then sutured in the usual manner and the catheter tied in place with the black silk sutures that have been used to close the incision. The catheter is occluded with a silver clip near the scalp, and the cut end, which is usually 7 cm. from the place it

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emerges from the scalp (fig. 1), is attached to the black silk sutures that have been used to close the incision on the opposite side of the scalp. This allows a small dressing to cover the incision, and the patient is taken to the x-ray room, where the ventriculographic studies are completed (fig. 2 *A* and *B*). If the ventricular system is incompletely filled, and it seems

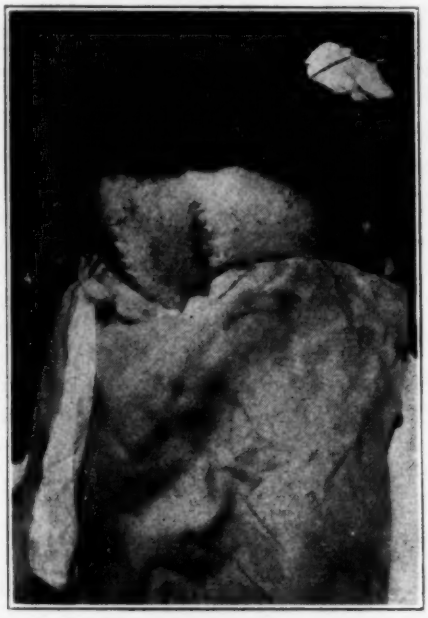

Fig. 1.—Sutured incisions with catheter and attached sterile rubber bag (condom). A silver clip can be seen occluding the catheter just above the attachment of the bag. The catheter can be opened and closed at will.

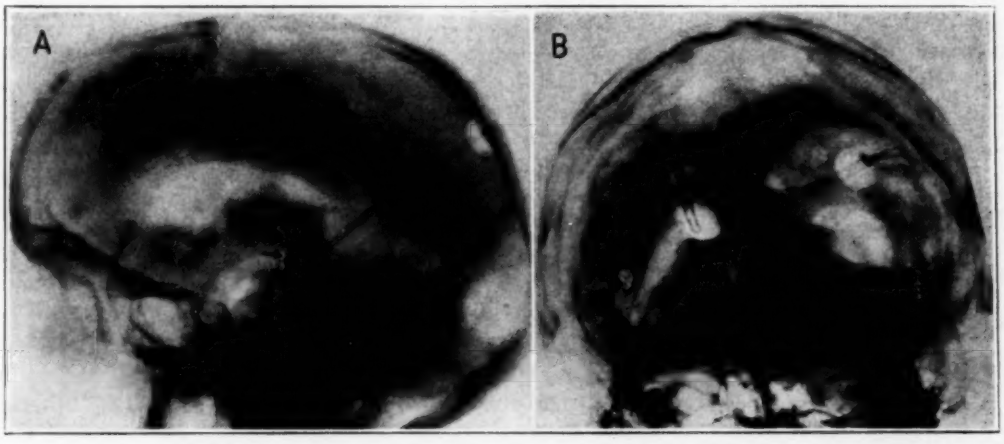


Fig. 2.—Lateral (*A*) and posteroanterior (*B*) ventriculograms, demonstrating catheter in the ventricle.

advisable to insert more air, this can be done by means of the catheter with the patient on the x-ray table, without his being transported back to the operating room. As soon as the ventriculograms have been read, the patient is returned to the operating room and the catheter is opened, the accumulated air and fluid being allowed to escape. The ventricle is allowed to drain throughout the craniotomy, so that all the available decompression is utlized; this simplifies the opening of the dura without fear of rupture of the cortex. It also allows a

more normal circulation of the brain tissue than would be possible if the cortex were bulging through the opening made in the dura.

In the employment of ventricular drainage, it must be remembered, of course, that if the entire ventricular system is occluded and little fluid escapes, its decompression value is of little help. On the other hand, the escape of even 5 cc. of fluid may be of great aid. The collapse of ventricles occurs only infrequently, usually in cases of tumors that involve the corpus callosum or the midline. Since the institution of ventricular drainage during craniotomy, no rupture of the cortex due to increased intracranial pressure has occurred after the dura was opened.

After craniotomy is completed, the catheter is closed for a few hours, with the idea that a moderate amount of intracranial pressure may prevent postoperative venous oozing of blood. After a few hours the catheter is opened and a sterile soft rubber bag (condom) is tied to the end of the catheter, a soggy, moist head dressing being thus prevented. This bag also tends to take care of the fluctuating intracranial pressure in that it can be readily emptied with a sterile hypodermic needle attached to a syringe. The rubber bag is strategically placed in the head dressing so that one can readily observe distention with fluid or can determine whether the fluid is draining properly. Occasionally it is necessary to manipulate the catheter slightly to make it drain properly. If this does not suffice, a syringe with sterile saline solution can be used to irrigate the catheter gently.

This procedure obviates frequent ventricular taps, with the resulting sudden changes in intracranial pressure, and tends to keep the pressure at a more uniform level. At the end of the second postoperative day the catheter is occluded for a period of twelve hours; if the intracranial pressure is tolerated by the patient, the catheter is opened, the fluid allowed to escape and the catheter removed.

The catheter has been allowed to remain in a ventricle as long as twelve days without known ill effects. Rarely is it necessary to decompress the ventricular system for more than three days, and usually not that long after the removal of a cerebral tumor. Obviously this method of drainage accomplishes everything that was formerly done by decompression and makes it possible to close the dura and replace the bone flap without bony defect.

The method described here is not a new procedure in any sense except in its application as a routine measure.

It has been used with well over 500 patients, without known untoward effects. There has been no evidence of infection.

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SPECIAL ARTICLE

# GENERAL PRINCIPLES OF AUTONOMIC INNERVATION

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Work of the last twenty years has thrown increasing light on the function of the autonomic nervous system and the control of its activity by cerebral influences. Much of the new body of data is still incomplete and controversial. This gives one an opportunity to review the general principles of autonomic innervation and the relationship of sympathetic and parasympathetic influences.

## NOMENCLATURE

The autonomic nervous system is also called the sympathetic, or involuntary, nervous system. Langley [1] introduced the term autonomic, calling the two subdivisions the sympathetic and the parasympathetic. His seems the clearest means of designation. Although this nomenclature has been widely accepted, many standard textbooks still employ confusing terminology. Thus, Ranson [2] has a chapter devoted to the sympathetic nervous system. Under a subheading he stated:

> For many reasons it is convenient to have a name which will designate the sum total of all general visceral neurones, both preganglionic and postganglionic, whether associated with the cerebral or spinal nerves. For this purpose the term "autonomic system" is in general use.

The difficulty in terms is related to the anatomic delimitation of the autonomic nervous system. This system was early considered to consist of preganglionic cells, lying in the spinal cord and brain stem, and postganglionic neurons, gathered in peripheral ganglia. Thus, it was defined as a purely motor system. With later emphasis on reflex arcs, the importance of the afferent side of the reflex arc received more attention. Later, autonomic control by higher centers in the brain became the subject of investigation. Thus, various authors have employed special names to emphasize their particular point of view.

## AFFERENT FIBERS FROM SMOOTH MUSCLE AND GLANDULAR TISSUES

Many afferent fibers end in the smooth muscle and glandular tissues of the body. Large numbers of these sensory fibers are myelinated, although Ranson included unmyelinated fibers. These fibers have their cells of origin in the sensory ganglia of the spinal and cranial nerves. No sensory cells have been demonstrated in the autonomic ganglia; so no reflex arc is mediated through the peripheral autonomic nervous system.

Morphologically, the sensory endings in the viscera are of several types. First, in the smooth muscle of the constrictor of the pupil (Langworthy and Ortega [3]) and of the stomach, urinary bladder (Kleyntjens and Langworthy [4]) and bronchi

From the Henry Phipps Psychiatric Clinic, Johns Hopkins University.

1. Langley, J. N.: The Autonomic Nervous System, Brain **28**:1-26, 1903.
2. Ranson, S. W.: Anatomy of the Nervous System, Philadelphia, W. B. Saunders Company, 1943.
3. Langworthy, O. R., and Ortega, L.: The Iris, Medicine, to be published.
4. Kleyntjens, F., and Langworthy, O. R.: Sensory Nerve Endings on the Smooth Muscle of the Urinary Bladder, J. Comp. Neurol. **67**:367-380, 1937.

(Larsell and Dow [5]) myelinated fibers end in complicated, spindle-shaped terminations, which appear to be stretch receptors, similar to proprioceptive neuromuscular and neurotendinous spindles seen in striated muscle. The endings in smooth muscle do not have a well formed connective tissue capsule. The smooth muscle reacts to stretch stimuli, and the tone of the muscle is maintained by the afferent stimuli from the muscle itself. This is illustrated by the abnormal function of the vesical muscle in patients with tabes dorsalis (Langworthy, Kolb and Lewis [6]). This disease causes degeneration of the sensory proprioceptive fibers. Under these conditions the tone of the vesical wall is decreased, owing to the loss of proprioceptive stimuli. The muscle is stretched passively, inasmuch as the patient no longer recognizes when the bladder is full and so permits overdistention. The poor contraction of the muscle is reflected in the presence of a residuum of urine. The patient has difficulty in micturition, expressed as hesitancy and incontinence.

Second, myelinated sensory nerve fibers terminate on blood vessels or on structures in their immediate vicinity. Woollard [7] observed sensory endings on the small arteries, particularly the arterioles. In the iris, I noted complicated sensory endings stretching out over the capillaries, particularly those near the pupillary border. Woollard noticed that the sensory nerve fibers on the blood vessels gave rise to branches which ended on fat cells or in encapsulated nerve endings close to the vessel. He expressed the belief that stimuli from these endings have a part in control of vascular tone. Sheehan [8] stated the opinion that the encapsulated nerve endings in the mesentery were delicate mechanisms designed to respond to changes in blood pressure. The importance of the role of afferent fibers on blood vessels in control of the circulation has never been investigated.

Third, myelinated fibers give rise to great numbers of club-shaped endings on the peritoneal surface of the bladder and stomach and over the outer surface of the iris. One fiber branches many times and supplies endings to a large area.

Finally, the mucosal layer of the viscera receives abundant nerve endings, many of which are probably sensory. These have received little study. The mucosa of the stomach and the urinary bladder are said to be slightly sensitive to extremes of heat and cold. They give responses to pain, but touch is poorly perceived.

In summary, the normal function of smooth muscle is partially dependent on stretch stimuli from the muscle itself. It may be assumed that sensory fibers end in all smooth muscle and glandular structures of the body, so that a complete reflex arc for control of their activity is provided. Little is known at present concerning the sensory fibers. Their cells of origin lie in the sensory and spinal ganglia, not in the peripheral autonomic ganglia. The function of the autonomic nervous system is influenced by sensory stimuli from all portions of the body. Thus, painful stimulation of the sciatic nerve will cause the pupil to dilate. The sympathetic portion of the autonomic nervous system is particularly responsive to emotional states.

### ANTAGONISM OF SYMPATHETIC AND PARASYMPATHETIC INFLUENCES

The statement is commonly accepted that the sympathetic and the parasympathetic portion of the autonomic nervous system have antagonistic functions. Their

5. Larsell, O., and Dow, R. S.: Innervation of the Human Lung, Am. J. Anat. **52**:125-146, 1933.

6. Langworthy, O. R.; Kolb, L. C., and Lewis, L. B.: Physiology of Micturition, Baltimore, Williams & Wilkins Company, 1940.

7. Woollard, H. H.: The Innervation of Blood Vessels, Heart **13**:319-336, 1926.

8. Sheehan, D.: The Clinical Significance of the Nerve Endings in the Mesentery, Lancet **1**:409-412, 1933.

activities are believed to have exactly opposing results on the organs which they control. This is emphasized by diagrams in many books showing their influence in decreasing or increasing the activity of different structures of the body. Personalities and groups of psychoneurotic symptoms have been classified on the basis of sympathetic or parasympathetic overfunction. I believe that this concept is erroneous, and the results of experimental studies will be marshaled as proof. The sympathetic and the parasympathetic system have different functions which normally are correlated. The significant activities of the sympathetic and the parasympathetic group of fibers will be discussed later.

The theory of antagonism in the functions of the two portions of the autonomic nervous system has been applied to most organs supplied by the two groups of nerves. In the case of the urinary bladder the sympathetic fibers are referred to as the nerves concerned with filling of the bladder. They are thought to close the internal vesical sphincter and to relax the musculature of the wall. The parasympathetic fibers are sometimes called the nerves controlling the emptying of the bladder. They are said to cause the internal vesical sphincter to relax and the vesical muscle to contract.

Experimental studies lead to different conclusions. Section of the sympathetic fibers has no significant effect on the urinary bladder, which acts as well as ever. Section of the parasympathetic fibers paralyzes the bladder completely. Later, function may partially return, but it is imperfect.

In the case of the blood vessels, the sympathetic system is considered to supply vasoconstrictor influences, and the parasympathetic system, vasodilator influences. There is no clear evidence that the peripheral vascular system receives a parasympathetic innervation or that it has a separate innervation producing vasodilatation. It is probable that control through the sympathetic fibers can either increase or decrease vascular tone. Stimulation of the posterior, or sensory, nerve roots causes vasodilatation in a corresponding segment of the body. This is an abnormal, antidromic stimulation, releasing chemical mediators at the periphery.

### ANTAGONISTIC INNERVATION IN CONTROL OF THE PUPIL

The pupillary reactions will be analyzed at some length because there is no structure in which the antagonism of the two groups of fibers has been more widely accepted than in the iris. It is usually stated that the parasympathetic fibers reaching the iris by way of the oculomotor nerve and the ciliary ganglion supply the constrictor muscle of the iris and by producing its contraction bring about constriction of the pupil. On the other hand, the sympathetic fibers, with their relay station in the superior cervical ganglion, are believed to innervate a dilator muscle of the iris, which by its contraction tends to enlarge the pupil. Correlation between the two balanced systems, therefore, determines the size of the pupil at any particular moment.

In support of the idea that the sympathetic and the parasympathetic fibers innervate different mechanisms which have opposing effects on the size of the pupil of the eye, the following positive observations must be taken into consideration: Stimulation of the oculomotor nerve produces constriction of the pupil, and section of this nerve causes the pupil to dilate to a maximal degree. On the other hand, stimulation of the sympathetic fibers causes the pupil to dilate, and section of these fibers gives rise to constriction of the pupil, so that it becomes somewhat smaller than the one on the opposite side. However, the constriction which follows section of the sympathetic nerves is by no means a maximal one. Recent physiologic studies have shown that reflex responses of the iris producing changes in the

diameter of the pupil are mediated largely, if not entirely, through the parasympathetic pathway. Pain may possibly produce reflex dilatation of the pupil through the sympathetic pathway, but even this dilatation may be largely a response to epinephrine. Reflex dilatation of the pupil is dependent to a great extent on relaxation of the constrictor muscle of the iris.

Ury and Gellhorn [9] expressed the belief that dilatation of the pupil in response to emotional stimuli is effective through inhibition of the third nerve, since this form of stimulation evokes immediate dilatation in the sympathectomized pupil but fails to do so when the oculomotor nerve is cut.

Ury and Oldberg [10] stated that reflex dilatation of the pupil in response to pain is mediated solely by central inhibition of the parasympathetic innervation. They found that none of the responses of the pupil to efferent stimuli is lost when the sympathetic component is cut but the magnitude of the reaction is diminished. This difference in response is due to the normal tonic action of the sympathetic fibers, and not to their reflex excitation. The dilatation dependent on excitation of the sympathetic fibers to the iris is an invariable response and is not affected by any reflex changes.

Bain, Irving and McSwiney [11] used dilatation of the pupil as an index in determining the presence of pain fibers in the splanchnic nerves. From their experiments they came to the conclusion that this dilatation depends on a pathway through the nucleus of the third nerve (parasympathetic).

Seybold and Moore [12] attempted to evaluate the role of sympathetic and parasympathetic fibers in pupillodilatation. Their experiments made it apparent that the activity of the parasympathetic fibers contributes the principal factor in the reflex pupillodilatation elicited by withdrawal of light, painful stimuli and emotional excitement. Under ordinary conditions sympathetic tone in the dilator muscle is remarkably constant, while parasympathetic responses are subject to extreme reflex modification. Consequently, changes in the size of the pupil depend on reflex variation in the activity of the parasympathetic fibers. Section of the sympathetic fibers effects diminution in the extent of reflex dilatation.

In summary, the assumption of two antagonistic muscles balanced against each other, innervated by two distinct sets of autonomic nerve fibers, is not required to explain the movements of the pupil. Instead, contraction of the constrictor muscle can be increased or decreased to produce the desired effect.

The need for the assumption of a dilator muscle to serve as antagonist to the constrictor muscle was not felt until the end of the nineteenth century. Anatomists have never clearly demonstrated an adequate group of muscle fibers to serve as a dilator muscle in the iris. Anatomists and physiologists were first content to explain the movements of the pupil by turgescence of the spongy vascular tissue of the iris. It was noticed that the pupil responded to the pulse with small fluctuations, and it was assumed that dilatation and constriction of the vascular bed had an important influence on the pupil. Contraction of the pupil was related to dilatation of the vessels, and dilatation of the pupil, to their contraction.

When the constrictor muscle was discovered, its contraction and relaxation were used to explain the movements of the pupil. Many investigators found this explana-

9. Ury, B., and Gellhorn, E.: Role of the Sympathetic System in Reflex Dilatation of the Pupil, J. Neurophysiol. **2**:268-275, 1939.

10. Ury, B., and Oldberg, E.: Effect of Cortical Lesions on Affective Pupillary Reactions, J. Neurophysiol. **3**:201-213, 1940.

11. Bain, W. A.; Irving, J. T., and McSwiney, B. A.: The Afferent Fibers from the Abdomen in the Splanchnic Nerves, J. Physiol. **84**:323-333, 1935.

12. Seybold, W. D., and Moore, R. M.: Oculomotor Nerve and Reflex Dilatation of the Pupil, J. Neurophysiol. **3**:436-441, 1940.

tion insufficient. The old idea appeared under a new form, and an important role in dilatation of the pupil was attributed to the blood vessels. Langley and Anderson,[13] on the basis of rather obscure arguments, many of which are no longer valid, stated that there was need for a distinct dilator muscle of the iris.

It must be realized that dilatation of the pupil has never been clearly related to a specific muscle. One group of anatomists expressed the belief that there was no dilator muscle; another asserted that the dilator muscle was made of radial smooth muscle fibers, which were distinct one from the other and were situated in the posterior portion of the stroma of the iris. A third group stated the belief that the dilator muscle was represented by a muscular membrane, which lay on the posterior surface of the stroma of the iris, just anterior to the inner layer of pigmented epithelium, and which they called a posterior limiting membrane. This muscular membrane is described today as the dilator muscle of the pupil.

Studies have shown that the iris is an extremely vascular structure, containing the ciliary bodies, with their medial and lateral prolongations (Langworthy and Ortega [3]). The medial prolongations of the ciliary processes extend inward toward the pupillary margin. The blood vessels are tortuous and have somewhat the structure of coiled springs. Apparently, the blood vessels, by dilating and contracting, change to a considerable extent the contour of the ciliary bodies and, secondarily, the width of the iris and the size of the pupil. These blood vessels are controlled by sympathetic nerve fibers. In preparations in which the sympathetic fibers to the pupil had been cut some days previously, the pupil was more constricted and there was greater dilatation of the blood vessels in the wall of the iris than in the opposite, normal eye.

Many of the phenomena ascribed to the sympathetic nerve–muscle action can be explained by changes in the caliber of the blood vessels or by contraction of the smooth muscle in their walls. The attempts of my associates and myself to inject the blood vessels of the iris with india ink and methylthionine chloride gave results which bear on this question. In making these injections, we endeavored to keep the pressure of the fluid which was introduced through the heart at approximately that of the normal blood pressure of the animal. In order to make the injection complete, however, it was often necessary to increase the pressure somewhat or to cut down the outflow of the fluid through various channels, so that the vascular system was distended with fluid. Under these conditions, the size of the pupil could be altered at will by changing the pressure of the fluid entering the vascular system. When the pressure of flow into the heart was increased, the pupil became smaller, whereas when the pressure was decreased, the pupil immediately enlarged.

It is probably fair to assume that in normal persons the size of the pupil is influenced to some extent at least by the circulation through the iris. The shape of the pupil may be altered by unequal injection of different portions of the iris. In the area where the vessels were injected with ink, the iris expanded and the pupillary margin became flattened, whereas the iris was narrower and circular in portions of the iris in which injections were not well done.

In summary, reflex control of the pupillary diameter is mediated almost, if not entirely, through the parasympathetic fibers. If there is any dilator muscle present in the iris, it has little, if any, role in the normal phasic activity producing changes in the size of the pupil. The sympathetic dilator mechanism furnishes a general tonic background, on which phasic movements of constriction or dilatation act only as long as the stimulus is applied. The sympathetic fibers appear to influence the pupil

13. Langley, J. N., and Anderson, H. K.: On the Mechanism of Movements of the Iris, J. Physiol. **13**:554-597, 1892.

through the medium of the blood vessels of the iris. The amplitude of pupillary movements is diminished after section of the sympathetic fibers to the iris, but all reflex responses are still present. There is no real antagonism of sympathetic and parasympathetic influences acting on the iris and pupil.

### FUNCTION OF THE SYMPATHETIC PORTION OF THE AUTONOMIC SYSTEM

The sympathetic and the parasympathetic portion of the autonomic nervous system do not have antagonistic functions, but they do have different activities, which are often correlated.

The sympathetic fibers reach all portions of the body, whereas the parasympathetic nerves supply only limited areas. The preganglionic sympathetic fibers are given off from all the thoracic and from the upper lumbar segments of the spinal cord and travel for considerable distances in the paravertebral sympathetic trunk. One preganglionic fiber may end around cells in several segmental paravertebral ganglia. This distribution facilitates a diffuse response of the postganglionic sympathetic neurons. Indeed, the sympathetic system tends to react as a whole, although different portions may be called into function separately.

The sympathetic fibers reach all the tissues of the body in their role of vasoconstrictor fibers to the blood vessels. There are no sympathetic endings on striated muscle, but the blood vessels of the muscle are under sympathetic control, and this regulation must exert considerable influence on muscle metabolism.

The function of the sympathetic system is much better understood than the influence of the parasympathetic system. Its activity is closely interwoven with that of the medulloadrenal system. Sympathetic fibers innervate the pupils, the sweat glands, the pilomotor apparatus and the blood vessels. The fibers, by their activity, mobilize the blood sugar, control the temperature and regulate the blood pressure. They innervate the medulla of the adrenal gland and other chromaffin tissue in the body.

The sympathetic system is largely an emergency mechanism, responding strongly to emotional stimuli of rage and fear. Emotional excitement and cold produce similar bodily changes, manifested as restlessness, trembling and shivering. The sympathetic system responds also to pain, muscular exercise and hypoglycemia after the administration of insulin.

Cannon [14] found that animals survived when almost all of the peripheral sympathetic ganglia had been removed. The animals could exist well in a neutral atmosphere but could no longer respond adequately to emotional stimuli, extremes of cold or other stimuli just mentioned.

There is abundant evidence that the sympathetic system is controlled by reflexes through the hypothalamus. Stimulation or localized injuries of the hypothalamus have a profound effect on blood pressure, control of temperature and sugar metabolism. An uncrossed pathway, extending from the hypothalamus to the spinal cord, has been identified.

Bard [15] demonstrated that removal of both cerebral cortices and portions of the diencephalon, with the hypothalamus left intact, produced startling changes in the behavior of cats and dogs. A slight stimulus, such as pinching the tail, produced violent reactions of rage and a mass discharge of activity by the sympathetic nervous

14. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, ed. 1, New York, D. Appleton and Company, 1915; ed. 2, 1929.

15. Bard, P. A.: Diencephalic Mechanism for the Expression of Rage with Special Reference to the Sympathetic Nervous System, Am. J. Physiol. **84**:490-515, 1928.

system. This "sham rage" is apparently dependent on a release of the sympathetic mechanism from control by higher centers in the brain.

In summary, sympathetic fibers are distributed to all portions of the body. The sympathetic system is designed to react as a whole as an emergency mechanism in response to pain, cold and emotional states.

### FUNCTION OF THE PARASYMPATHETIC PORTION OF THE AUTONOMIC NERVOUS SYSTEM

The functions of the parasympathetic portion of the autonomic system have never been as clearly defined as those of the sympathetic portion. Parasympathetic fibers are given off only from localized portions of the brain and spinal cord. They arise from the brain stem with the oculomotor, the facial, the glossopharyngeal, the vagus and the bulbar portion of the accessory nerve and from the sacral portion of the spinal cord and supply certain definite structures. The cranial outflow sends fibers to the constrictor muscle of the pupil, the salivary glands, the heart, the lungs and the upper portion of the gastrointestinal tract. The sacral outflow innervates the lower portion of the gastrointestinal tract, the urinary bladder and the erectile organs. Thus, the parasympathetic neurons supply only special structures in the body, in contrast to the sympathetic fibers, which reach all structures, at least in their function of vascular control.

Cannon [14] summarized the parasympathetic functions as follows:

> The cranial and sacral preganglionic fibers resemble thus the nerves to skeletal muscles, and their arrangement provides similar possibilities of specific and separate action in any part, without action in other parts.

Cannon supported the theory of antagonism of function between the sympathetic and the parasympathetic neurons, expressing this antagonism in the following terms:

> To the cranial division of the visceral nerves, therefore, belongs the quiet service of building up reserves and fortifying the body against times of need and stress. . . . Like the cranial division, the sacral is engaged in internal service to the body, in the performance of acts leading to greater comfort. . . . It is, therefore, the natural antagonism between those two processes in the body— . . . between preparation and use, between anabolism and catabolism—and the correlated antagonism of the central innervations, that underlie the antipathy between emotional states which normally accompany the process. . . .
>
> A summary in few words of the chief functions of each division of the autonomic would designate the cranial division as the upbuilder and restorer of organic reserves, the sacral as the servant of racial continuity, and the sympathetic as the preserver of the individual.[14]

In a discussion of Cannon's summary, the first statement is worthy of amplification: "The cranial and sacral preganglionic fibers resemble thus the nerves to skeletal muscles." One gains the impression that the parasympathetic system is subject to more elaborate control by the central nervous system than the sympathetic fibers. This statement will be developed in greater detail in the pages which follow. Just as there are many degrees of differentiation in muscle fibers—smooth muscle; cardiac muscle; red, striated muscle fibers rich in sarcoplasm, and other, more quickly contracting, muscle fibers poor in sarcoplasm—so there are degrees of differentiation in nerves. The sympathetic nervous system is relatively primitive, resembling to some degree the primitive nerve net of invertebrates. The parasympathetic nervous system is more highly differentiated, being designed for certain special uses and under reflex control at different levels in the central nervous system. For example, the urinary bladder apparently may be made to respond voluntarily either in the direction of contraction or of relaxation of the vesical muscle, micturition being thus initiated or postponed. Its activity is regulated by

stretch receptors in the muscle itself, and when these receptor neurons are injured, function is abnormal.

I have speculated whether it would be possible to recognize differences in structure between the sympathetic and the parasympathetic postganglionic nerve fibers and their endings in the peripheral portions of the body. It is probable that such a differentiation could be made. The constrictor muscle of the pupil is supplied by parasympathetic neurons. In the muscle the nerve fibers run parallel with the muscle fibers and give rise to many nerve endings on these fibers. These endings, although smaller, are similar to the motor endings on striated muscle. In the same area the blood vessels are supplied by sympathetic neurons. These fibers cross and recross, having much the picture of a network. They give off branches terminating in small bulbous endings on the muscle of the arteries and on the endothelial cells of the capillary wall.

The statement by Cannon concerning the function of the different types of fibers suggests more specific activities for the parasympathetic fibers. These fibers can act on one organ without producing a diffuse effect on all the structures which they innervate. Cannon suggested an antagonism of function between these two systems of fibers, which was exaggerated.

The function of the parasympathetic portion of the autonomic nervous system may be stated as follows: Parasympathetic nerves have primarily the function of control. They regulate the tone and contraction of smooth and cardiac muscle in a way similar to the control of striated muscle by somatic motor fibers. They are influenced by reflex arcs through different portions of the central nervous system in a manner similar to that in which somatic motor fibers to striated muscle are controlled.

## CONTROL OF PERIPHERAL STRUCTURES BY THE PARASYMPATHETIC NERVOUS SYSTEM

In discussion of the control exerted by parasympathetic fibers, I shall use illustrations from my experience with the constrictor muscle of the pupil and the musculature of the urinary bladder. Characteristic changes in the tone and contraction of the urinary bladder occur after specific injuries of portions of the peripheral or the central nervous system.

An organ such as the urinary bladder offers the possibility of accurate quantitative estimations of muscular tone and contraction. The muscle has the ability to accommodate different amounts of urine without great change in intravesical pressure up to the physiologic limits of distention. The pressure in the empty bladder is approximately 2 cm. of water, and the pressure in the human bladder containing 400 cc. of urine may be not more than 6 or 8 cm. of water. This demonstrates the remarkable adaptive ability of the muscle. This ability to accommodate widely different volumes at approximately the same pressure is less evident after section of the parasympathetic fibers. It is influenced little, if at all, by section of the sympathetic portion of the vesical innervation.

The muscle of the bladder is capable of a prolonged contraction sufficient to empty the viscus completely. This sustained contraction is dependent on the parasympathetic influence. During the later stages of normal vesical filling, small waves of contraction occur which give conscious information that the organ is reaching the limits of its capacity. These contractions may normally be controlled by voluntary effort through the parasympathetic system.

The vesical function has been studied after section of the preganglionic parasympathetic fibers. Under this condition the vesical activity is dependent on the

intrinsic power of contraction present in smooth muscle fibers, the influence of the peripheral postganglionic parasympathetic neurons which are present in the viscus and the sympathetic innervation. Now, during the process of vesical filling there are continuous small waves of vesical contraction, which are apparently dependent on the asynchronous contraction of different portions of the muscle composing the wall. Fluid is likely to escape from the bladder at the height of each of these contractions.

In summary, the parasympathetic influence controls the tone and contractions of the vesical muscle during the period of vesical filling. It is possible voluntarily to suppress waves of vesical contraction through the mediation of the parasympathetic pathway. The parasympathetic influence can induce a sustained contraction of the muscle which empties the bladder completely. Influences through the sympathetic pathway appear to have no part in the control of any of these activities.

The constrictor muscle of the iris is completely paralyzed after section of the parasympathetic fibers. The pupil is maximally dilated and no longer responds to reflex stimuli. The constrictor muscle of the iris, for this reason, differs from the vesical muscle, which maintains some independent power of contractility after section of the nerve supply. There are several possible explanations. The postganglionic parasympathetic neurons lie in the bladder wall and are uninjured by section of the preganglionic fibers. The postganglionic cells innervating the pupil lie in the ciliary ganglion and may be removed at operation. However, section of the preganglionic fibers in the oculomotor nerve, with the postganglionic cells left intact, gives the same result.

The difference in reactions of the two muscle groups to section of their parasympathetic innervation makes it possible, and necessary, to discuss further the degrees of differentiation of nerve and muscle. In birds the constrictor of the iris is made up of striated muscle and is innervated by myelinated fibers similar to those supplying striated muscle elsewhere in the body. While in mammals the constrictor of the iris is made up of smooth muscle, this muscle responds to section of the nerve supply in a manner similar to striated muscle. This is all the more interesting in that the vesical muscle appears to be either directly or indirectly under voluntary control, whereas the constrictor of the pupil is under little voluntary control. However, the pupil does constrict as a part of the general convergence response, which can be initiated voluntarily. It is possible that both the pupil and the bladder are under voluntary control to the extent that the smooth muscle takes part in a complex movement which also requires striated muscle and is initiated through the medium of the striated muscle.

There is certainly some evidence that the muscle innervated by the parasympathetic fibers is more dependent on its control from the central nervous system than is muscle innervated by sympathetic fibers. After removal of the majority of the postganglionic sympathetic cells the circulation is maintained adequately. After section of the parasympathetic fibers the function of the urinary bladder is grossly abnormal. It has been shown that animals with most of the sympathetic fibers cut can survive in a neutral environment. Removal of all the parasympathetic fibers would produce marked and disabling disturbances.

Consideration of the parasympathetic innervation as a control mechanism may be applied again to the heart. The effect of these fibers is to slow the rate. In the gastrointestinal tract the effect of the parasympathetic fibers is to slow the peristaltic waves. It permits the accumulation of waste products in the lower part of the bowel and provides the mechanism for their periodic expulsion.

### CONTROL OF THE PARASYMPATHETIC SYSTEM BY REFLEXES MEDIATED THROUGH THE CENTRAL NERVOUS SYSTEM

The urinary bladder offers an unusual opportunity for study of the control of smooth muscle by parasympathetic influences, inasmuch as it is possible to record accurately changes in tone and contraction in the wall by studying the changes of pressure in the cavity of the bladder. The observations in our experiments were recorded in centimeters of water.

It has been mentioned earlier that the function of the vesical muscle is dependent on impulses from stretch receptors in the muscle. The stretch impulses are carried by myelinated fibers which enter the posterior sacral roots. The nerve cells lie in the spinal ganglia. Section of the posterior sacral roots produces most severe vesical disability. Retention of urine is followed by overflow incontinence. No waves of vesical contraction occur. The organ becomes greatly distended, and the wall is stretched thin.

Section of the parasympathetic fibers to the bladder produces a different type of abnormality. Small waves of vesical contraction occur at fairly regular intervals during the period of filling. These waves are dependent on contraction of portions of the muscle at one time. A small amount of fluid escapes from the bladder at the height of one of these waves of contraction, but the contraction is poorly sustained and the bladder never empties completely.

Transection of the spinal cord above the sacral segments has a profound effect on vesical function. There is, of course, retention during the period of shock. Later, vesical contractions are elicited by stimuli reaching the sacral portion of the cord. Large waves of vesical contraction can be induced by stimuli applied to the perineal region, but these contractions are seldom sustained well enough for the bladder to be emptied completely. Reflex contraction of the external vesical sphincter may stop micturition and lead reflexly to suppression of contractions in the vesical wall.

Characteristic disturbances follow injury of the cerebral motor cortices or the corticospinal pathways bilaterally. These disturbances are most clearly observed in patients, inasmuch as the cerebral motor cortex is highly differentiated in man. The patient complains of urgency and frequency of micturition. Incontinence may occur at times because he cannot voluntarily control or suppress vesical contraction. The stretch reflex in the vesical muscle is overactive. The sudden introduction of a quantity of fluid into the bladder elicits the stretch reflex and often causes the organ to empty completely. The muscle will tolerate less than the normal distention, so that micturition is more frequent. The violent stretch contractions can no longer be suppressed by voluntary effort, with resulting urgency and incontinence. Thus, in smooth muscle, as in striated muscle, the stretch reflex is exaggerated by release from control of the cerebral cortex.

Characteristic changes in the tone and contraction of the bladder are also observed in patients with the parkinsonian syndrome. The patient complains of urinary frequency. The intravesical pressure is unusually high during the period of vesical filling. There is no overactivity of the stretch reflex. The wall will not permit the normal degree of distention.

The constrictor muscle of the pupil does not lend itself as well to studies of changes in tone and contraction as does the vesical muscle. It is possible only to observe changes in size of the pupil after injuries to the central nervous system. Sometimes the parkinsonian syndrome is manifest almost entirely on one side of the body. Provided the patient is not taking drugs of the atropine series, the pupil is smaller and reacts more sluggishly on the side of the body on which the rigidity

is manifest. During the first few weeks after the onset of hemiplegia the pupil may be larger on the paralyzed side of the body. Later the pupils usually become of equal size.

### RELATION OF SYMPATHETIC AND PARASYMPATHETIC INNERVATION IN A SINGLE ORGAN

It has been shown that section of the sympathetic fibers has little influence on the reflex contraction or dilatation of the pupil except for decrease in the amplitude of the response. Similarly, the function of the urinary bladder is not disturbed by section of the sympathetic nerve supply.

What function do the sympathetic fibers mediate when both sympathetic and parasympathetic fibers innervate the same organs? I believe that in this case the sympathetic innervation is solely concerned with the blood supply whereas the parasympathetic fibers supply the smooth muscle of the viscus. In the iris the parasympathetic fibers innervate the constrictor muscle, while the sympathetic fibers innervate the vessels of the ciliary bodies and the iris. A study of stained preparations after differential section of sympathetic and parasympathetic fibers tends to support this hypothesis (Langworthy and Ortega [3]).

### VOLUNTARY CONTROL OF SMOOTH MUSCLE INNERVATED THROUGH THE PARASYMPATHETIC SYSTEM

There is undoubtedly a direct or indirect voluntary control of certain of the smooth muscles innervated by the parasympathetic system. In this connection it should be borne in mind that movements, and not individual muscles, are represented in the cerebral cortex. Complex movements often require the combined activity not only of striated muscle but of smooth muscle and glandular tissue.

Certain organs composed of smooth muscle are represented at the level of the cerebral cortex (Fulton [16]). Stimulation or removal of the cerebral motor cortex influences tone and peristalsis in the stomach and gastrointestinal tract. Stimulation of the cerebral motor cortex of the cat with an electric current will at times suppress waves of vesical contraction and at others initiate strong waves of contraction.

The constrictor muscle of the iris is subject to little apparent voluntary control. However, stimulation of a localized area in the occipital lobe induces pupillary constriction. Also, constriction of the pupil is part of the complex voluntary movement of convergence and accommodation. In this case it might be maintained that the voluntary stimulus leads first to contraction of the internal rectus muscles, including convergence, and that the pupillary constriction is a secondary action elicited by the convergence.

Movements of striated muscle are often closely correlated with the activity of the smooth muscle innervated by parasympathetic nerves. Denny-Brown and Robertson [17] discussed this correlation in the urinary bladder. Contraction of the external, striated muscle sphincter leads reflexly to suppression of waves of contraction in the vesical muscle. On the other hand, these authors expressed the belief that voluntary micturition was initiated by relaxation of the striated muscle of the perineum, followed by strong contraction of the vesical muscle.

This observation was not investigated in the experiments in this laboratory. When the changes in vesical pressure were observed, it appeared that patients

16. Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1938.

17. Denny-Brown, D., and Robertson, E. G.: On the Physiology of Micturition, Brain **56**:149-190, 1933.

were able to suppress voluntarily the waves of contraction in vesical muscle. Similarly, stimulation of the cerebral cortex in the experimental animals at times suppressed, and at others initiated, vesical contraction.

In summary, then, the activity of structures innervated by parasympathetic fibers is intimately correlated with contraction of striated muscle closely associated with the organ concerned. Whether the cerebral cortex has a direct or an indirect control through the parasympathetic system is still a matter of speculation.

It may be said that the functions presided over by the parasympathetic system may have greater or lesser degrees of voluntary control. The urinary bladder is an example of unusually strong voluntary control. There is little evidence of voluntary control of the stomach, even though it is known that movements of this organ are represented at the level of the motor cortex.

## SUMMARY

Langley's designation of the autonomic nervous system as composed of sympathetic and parasympathetic components deserves universal acceptance in an effort to avoid confusion of terms. The autonomic system has been considered as purely a motor system, composed of preganglionic and postganglionic neurons. However, it is influenced by sensory impulses originating in the smooth muscle and glandular tissues, so that it operates on the basis of segmental reflex arcs. The normal function of smooth muscle is dependent on proprioceptive stimuli from the muscle itself. The autonomic fibers are also subject to control from all levels of the central nervous system, including the motor cortex.

The antagonism of function in organs which are innervated by both sympathetic and parasympathetic fibers has been exaggerated in the literature. The innervations of the iris and the vesical muscle are given to demonstrate that no real antagonism exists. The reflex movements of the pupil are dependent on contraction and relaxation of the constrictor muscle, which is innervated by parasympathetic fibers. The function of the urinary bladder is severely disturbed by section of the parasympathetic fibers and functions normally when the sympathetic fibers are cut. The functions of the two groups of nerves are correlated, and not antagonistic.

The functions of the sympathetic system have been carefully analyzed by Cannon and his co-workers. The sympathetic system is designed to respond as a whole, serving as an emergency mechanism which is responsive to cold and to emotional stimuli. Animals with most of the sympathetic fibers sectioned survive fairly well in a neutral environment.

The parasympathetic fibers are given off from the brain stem and the sacral portion of the cord and innervate only certain structures. Their function is more specific than that of the sympathetic system in that isolated portions of the parasympathetic innervation respond at one time. The parasympathetic system in many ways shows a greater differentiation than the sympathetic system. The peripheral endings of the parasympathetic fibers are possibly better developed and more specific. Although smaller, they are similar to motor endings on striated muscle. The peripheral sympathetic terminations resemble more closely a primitive nerve net. Parasympathetic fibers regulate the tone and contraction of cardiac and smooth muscle in a manner similar to the control of striated muscle by somatic motor fibers. The parasympathetic system is designed for special uses and is controlled at all levels of the central nervous system. In the urinary bladder, which is especially favorable for experimental study, characteristic changes of function occur after injury of the corticospinal pathways or in patients with

the parkinsonian syndrome. These abnormalities are analogous to the disturbances in striated muscle under the same conditions. Certain structures innervated by parasympathetic fibers are subjected, either directly or indirectly, to control from the motor cortex.

With future experimental studies there are likely to appear further distinctions between the sympathetic and the parasympathetic neurons, on the basis both of morphologic characteristics and of function. This differentiation may be quite as marked as that between somatic motor and autonomic fibers. The somatic motor fibers are of the highest differentiation, are most dependent on control through the central nervous system and are under the greatest voluntary control. The sympathetic fibers show the least differentiation, at least dependent on control through the central nervous system, and are least responsive to voluntary control. The parasympathetic fibers hold an intermediate position. When both sympathetic and parasympathetic fibers innervate a single organ, such as the iris, the urinary bladder or the gastrointestinal tract, it is probable that the sympathetic system exerts its influence solely through the medium of the circulation and the parasympathetic fibers through actual innervation of the smooth muscle.

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# Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

## Physiology and Biochemistry

AN ALCOHOL DETOXICATION MECHANISM IN THE CENTRAL NERVOUS SYSTEM. JOHN G. DEWAN, Am. J. Psychiat. **99**:565 (Jan.) 1943.

Dewan reports that nicotinic acid and riboflavin are components of a mechanism for alcohol oxidation in the brain. This mechanism may be used as a detoxicating or protective device when alcohol is used in narcotic concentrations.

FORSTER, Philadelphia.

ANTERIOR PITUITARY–STIMULATING ACTION OF YOHIMBINE. N. W. FUGO and E. G. GRASS, Endocrinology **31**:529 (Nov.) 1942.

Fugo and Grass found that the reports of experimental work on yohimbine are inconclusive as to the effect of the drug on the genital tract. They present further experimental evidence. Rats were treated by subcutaneous injections of yohimbine hydrochloride. Observations were made on the overt sexual behavior of the animals and on the effect on the estrus cycle by the vaginal smear method. Eventually gross and histologic studies of tissues were made. The results of the investigation indicate that the alkaloid yohimbine produces no precocious sexual development, that it has no direct effect on ovarian tissue and that it effects an excessive release of the luteinizing principle of the anterior lobe of the pituitary.

PALMER, Philadelphia.

STUDY OF EXCRETION OF PITUITARY HORMONES IN HUMAN URINE. G. E. SEEGAR JONES and N. L. R. BUCHER, Endocrinology **32**:46 (Jan.) 1943.

Modifications of the methods developed for investigation of crude pituitary extracts were used in a study of the proteins of human urine and their biologic activities. Specimens of the urine of menopausal women, of normally menstruating women and of normal men were concentrated and fractionated in such a way that the proteins were not destroyed or changed. These fractions were tested on hypophysectomized animals for the activities of various pituitary hormones. All types of specimens examined showed a biologic activity which corresponded to that of the follicle-stimulating principle of the anterior lobe of the pituitary. There was no evidence of activity of a luteinizing thyrotropic or adrenotropic principle in any fraction of any specimen studied. The active fraction was best precipitated from a saturated solution of ammonium sulfate at a $p_H$ of 6.8

PALMER, Philadelphia.

THE EFFECT OF HYPOPHYSECTOMY ON THE CONCENTRATION OF ASCORBIC ACID IN THE ADRENALS OF THE RAT. R. TYSLOWITZ, Endocrinology **32**:103 (Jan.) 1943.

Tyslowitz studied the concentration of ascorbic acid in the adrenals of the rat one to fifty-six days after hypophysectomy. He found a gradual decrease, which was shown also in the testis, liver, kidney and blood serum. Starvation alone reduced the ascorbic acid in the liver and kidney to a greater degree than in the adrenal, testis or blood serum. The results were similar for the male and for the female in both hypophysectomized and normal rats. The concentration of ascorbic acid in the adrenals of hypophysectomized rats was increased by treatment with suitable pituitary extracts. In rats with incomplete removal of the hypophysis the concentrations were high. Removal of the thyroid, in addition to hypophysectomy, failed to alter the results observed on treatment in hypophysectomized rats.

PALMER, Philadelphia.

THE PHYSIOLOGY OF THE LABYRINTH REVIEWED IN RELATION TO SEASICKNESS AND OTHER FORMS OF MOTION SICKNESS. W. J. MCNALLY and E. A. STUART, War Med. **2**:683 (Sept.) 1942.

McNally and Stuart have reviewed the entire literature on the physiology of the labyrinth, and they discuss the functions of the various parts in detail. The most important points may be summarized as follows: The semicircular canals are stimulated by angular acceleration. The stimulation of a canal is unidirectional; it elicits reactions of the head and body muscles necessary to compensate for any movement of the head in the plane of the canal.

Deflections of the cupula are responsible for nystagmus. The otoliths are stimulated by linear acceleration, or progressive movement. An otocyst can function without an otolith, but in animals normally possessing an otolith this organ modifies the reactions of the sensory hair cells and its absence produces disturbance of equilibrium. The saccule is not concerned with equilibrium but may be influenced by vibrational stimulation. The utricle is the most important gravity organ. It is stimulated by slow tilting about a horizontal axis, by centrifugal force and by linear acceleration. Its stimulation elicits all postural reflexes of the body and eyes previously allocated to both the saccule and the utricle. It is the end organ for the perception of linear acceleration. Vertical progressive linear acceleration is the most disturbing factor in the production of motion sickness. Centrifugal force stimulates the utricles, while the canals and saccules are unresponsive. Chronic increased intralabyrinthine pressure can damage the labyrinth, just as increased pressure produces choked disk. Mack's estimation of the threshold of labyrinthine stimulation for both angular and linear acceleration is still the standard for human beings.

Nystagmus does not occur in cases of seasickness. The question whether seasickness occurs in deaf-mutes and the reason for its absence need a great deal more investigation. The canals and the utricular otoliths are concerned in the body's response to sudden emergencies. They act as a check on each other in maintaining the degree of muscle tone necessary for formal posture and the normal reaction to sudden stimuli. The labyrinth is represented cortically in the posterior part of the temporal lobe. The vestibular nerve runs to the vestibular nuclei. From there the connections are widespread, especially with the cerebellum. Much more work is needed before these connections are fully understood. Opinions vary as to whether the labyrinth can become habituated to stimulation. If it can be, this habituation seems to be associated with the learning process.

PEARSON, Philadelphia.

## Psychiatry and Psychopathology

THE ROLE OF HEART DISEASE IN THE PSYCHOSES OF THE SENIUM. SAMUEL R. ROSEN and KARL L. SMITH, Am. J. M. Sc. **205**:48 (Jan.) 1943.

Rosen and Smith undertook to determine whether circulatory insufficiency plays a significant part in the relative cerebral anoxia associated with the senile psychoses. Forty-three patients with a psychosis associated with the senium were studied. These patients fell into three classes: (1) 16 patients with no evidence of cardiovascular disorder; (2) 15 patients with organic heart disease who were able to carry on ordinary activities and (3) 12 patients with heart disease accompanied by signs of congestive heart failure. The venous pressure and the arm to carotid circulation time were determined. The third class of patients showed abnormal values, whereas the first two classes had practically similar values, namely, venous pressures within the normal range and circulation times which were significantly elevated, but distinctly lower than the average. The results suggest that cardiac disorder does not play any significant role in the psychoses of the senium except as may be indicated by the moderate elevation of the circulation time.

MICHAELS, Boston.

METHODS OF ESTIMATING CAPACITY FOR RECOVERY IN PATIENTS WITH MANIC-DEPRESSIVE AND SCHIZOPHRENIC PSYCHOSES. EDWIN F. GILDEA and EVELYN B. MAN, Am. J. Psychiat. **99**:496 (Jan.) 1943.

Gildea and Man studied 142 patients with psychoses over a four to five year period and investigated the value of the lipid content of the blood serum as a prognostic method. For the manic-depressive patients with clearcut clinical pictures the usual clinical methods of prognosis were found dependable. With the schizophrenic patients such methods offered little more than pure chance, unless catatonic patients and those with queer excitement states were eliminated. The lipid, fatty acid and cholesterol contents of the serum were found to be associated in some degree with the capacity for recovery. High values for lipids were observed for most patients who recovered and low values for those who did not.

FORSTER, Philadelphia.

CLINICAL AND BIOLOGICAL INTERRELATIONS BETWEEN SCHIZOPHRENIA AND EPILEPSY. PAUL H. HOCH, Am. J. Psychiat. **99**:507 (Jan.) 1943.

Hoch investigated the incidence of seizures in 500 patients with schizophrenia. Of 2 patients who had convulsions, 1 suffered from post-traumatic seizures, and the other had pseudo-syncopal attacks during catatonic spells, with a normal electroencephalogram.

A review of 100 epileptic patients revealed 10 with symptoms resembling those of schizophrenia. Seven of these 10 patients presented additional symptoms of an organic psychosis.

On the basis of an investigation of the genetic factors both in schizophrenia and in epilepsy, Hoch concludes that while there is a genetically determined predisposition to each disease the two disorders are separate and unrelated disorders.

Of the electroencephalograms of 120 patients with schizophrenia, Hoch found 3 per cent with abnormalities suggestive of gross pathologic lesions. He concludes that the electroencephalographic evidence of a relation between epilepsy and schizophrenia is inconclusive and that the disease in schizophrenic patients who present definite abnormalities in the electroencephalogram may be considered a distinct entity.

FORSTER, Philadelphia.

RORSCHACH EXAMINATIONS IN ACUTE PSYCHIATRIC ADMISSIONS. KENNETH S. HITCH, J. Nerv. & Ment. Dis. **97**:27 (Jan.) 1943.

Hitch reports on a Rorschach analysis of 50 consecutive patients admitted to the psychiatric ward of the Station Hospital at Fort Dix, N. J. As compared with normal subjects, the psychiatric patients had a considerably lower number of total reactions. Good form responses were few and poor form responses frequent. The percentage of popular responses was about equal to that for a normal control group, while the percentage of original replies varied with the type of the patients. Lack of kinesthetic reactions and distortion of color values were characteristic and gave a clear picture of the primitive, infantile, egotistic adjustment of the group as a whole. Shading reactions occurred infrequently, while content responses varied little from normal except in their being usually restricted to commonplace subjects. There was no increase in the number of sexual responses. Typical psychotic reactions, such as contamination and positional responses, were presented only by relatively deteriorated patients. Card rejections were frequent, in contrast to the responses of normal subjects. Color shock was present in 30 per cent of the patients admitted. The validity of Piotrowski's signs of organic disease of the central nervous system was confirmed, as all patients with a psychosis of this type manifested at least five of the signs.

CHODOFF, M. C., A. U. S.

PSYCHOGENIC ILLNESS IN REGIMENTAL PRACTICE. W. L. JONES, Brit. M. J. **2**:338 (Sept. 19) 1942.

Jones discusses 42 cases of psychogenic illness in the British army observed during a period of twelve months, none of which occurred among front line troops. The series consisted of 19 cases of anxiety state, 21 cases of hysteria, 1 case of psychosis and 1 case of psychopathic personality. In 28 of the 42 cases the ages were between 20 and 30 years. The symptoms in order of frequency were headache, defective vision and effort syndrome. Jones emphasizes the importance of the patient's present being weighed against his potential value as a soldier, as well as the effect of such cases on morale. He calls attention to the fact that there are still soldiers who, though physically sound, are psychologically unfit for military service.

ECHOLS, New Orleans.

## Diseases of the Brain

SYMMETRIC NEVI OF FACE, TUBEROUS SCLEROSIS, EPILEPSY AND FIBROMATOUS GROWTH ON SCALP, WITH ABNORMAL ELECTROENCEPHALOGRAMS OF MEMBERS OF THE FAMILY. CHARLES K. GOOD and JOHN GARB, Arch. Dermat. & Syph. **47**:197 (Feb.) 1943.

Good and Garb report the case of an American-born woman aged 29 with an Italian mother and a French father, who were not consanguineous. A hairless, smooth, "red birth mark" was noted on the scalp at birth. At the age of 9 years this "mark" began to grow, increasing in diameter and thickness.

The patient was the second oldest of 6 girls. One sister, aged 21, was "nervous and irritable." Another, aged 15, had a congenital deformity of the cervical portion of the spine and unilateral deafness, which followed otitis. Another sister, aged 12, had bilateral nephroptosis, with angulation of the left ureter. The other members of the family presented nothing of interest. The serologic reactions of all the siblings were negative.

In the case cited, three small red "blotches" appeared first in the left malar region at 8 months of age. Similar lesions developed on the root of the nose and the right cheek and spread downward bilaterally to the mandible and chin. The maximum development of these lesions, numerically and in surface area, was attained at the age of 3 years. At 10 years of age the lesions began to grow, appearing as wartlike projections. After 16 years of age the mandibular lesions regressed, while the others became larger.

At the age of 4 years, the patient began to show signs of abnormal nervous irritability, such as supraorbital headache, frequent crying spells and attacks of stubbornness. These spells of stubbornness were followed by an abrupt change of mood, during which the patient became docile. At this time she began to have convulsive seizures. At 6½ years of age the typical

epileptic spells became distressing, one attack following another in rapid succession. At this time the condition reached a turning point, and general improvement followed. After this she never lost consciousness, but until within three or four months of the time of this report she had "nervous spells." The attacks of stubbornness persisted.

The lesion of the scalp appeared as a large, sharply demarcated, almost hairless, hard growth. The facial lesions were distributed in butterfly fashion and were pinhead-sized to split pea–sized. Intermingled with the lesions of the face were numerous pinhead-sized to hemp seed–sized fibromas. On the forehead were numerous yellowish brown spots. Many filiform, verrucous projections occurred along the right axilla.

Neurologically the patient showed hyperactive tendon reflexes and absence of the right plantar reflex. She had frequent episodes of absences associated with grimacing movements. She was easily irritated. A retrograde pyelogram revealed abnormalities of the right kidney and the left ureter. The electroencephalogram revealed diffuse abnormal cortical activity. A tracing made five months earlier revealed a borderline normal state. The patient had borderline intelligence. The histologic diagnosis of one of the lesions of the face was fibroma, and the lesion of the scalp was also interpreted as being of fibromatous structure.

The electroencephalogram of the father, aged 42, was interpreted as representative of a "latent" convulsive disorder; that of a sister, aged 22, displayed diffuse abnormal cortical activity. A sister, aged 18, showed diffuse cortical involvement, but to a lesser degree; a sister, aged 16, showed a mild degree of diffuse involvement.

The authors suggest that the electroencephalogram may prove valuable in the discovering of abortive types of tuberous sclerosis in members of a family and close or distant relatives of a person with epiloia. They point out that epiloia is frequently characterized by long remissions, during which the mental deterioration progresses after the convulsions have subsided.

SANDERS, Philadelphia.

NEUROLOGIC COMPLICATIONS IN THE MOTHER FOLLOWING PREGNANCY. THEODORE MELTZER, J. Nerv. & Ment. Dis. **96**:641 (Dec.) 1942.

Meltzer classifies the neurologic complications of pregnancy as those related to a pathologic pregnancy and those related to a healthy pregnancy. Under the first heading he includes eclampsia, chorea gravidarum and neuritis referable to the brachial plexus, probably toxic in nature. Under the second, he mentions neuritis involving the sacral plexus, the result of pressure of the fetus during labor; Simmonds' disease; sudden blindness, and hemiplegia, with or without aphasia. He reports the case of a 32 year old woman in whom, on her tenth postpartum day, right hemiplegia with aphasia suddenly developed, the condition persisting unchanged until her death, eighteen years later. Autopsy revealed that the left frontal lobe was completely replaced by a large cyst communicating with the lateral ventricle. The author believes that the etiologic agent responsible for this massive encephalomalacia was probably an air embolus, the air gaining access to the vascular system through the open uterine sinuses and passing through the pulmonary circulation to the left side of the heart and then to the brain.

CHODOFF, M. C., A. U. S.

MEDICAL ASPECT OF HEAD INJURIES. W. R. RUSSELL, Brit. M. J. **2**:521 (Oct. 31) 1942.

In 200 consecutive patients who had sustained head injuries the incidence of postconcussional symptoms was found to be much lower than is generally realized, and the duration of disability ranged from two to six months. Eighty-seven per cent of these patients returned to normal activities within six months. Russell lists the following complications of head injury which often cause unnecessary alarm: epileptic fits, delayed paralysis of the face, nuchal rigidity, bradycardia, papilledema, prolonged confusion or delirium and associated injuries. Neurologic examination is necessary to detect damage to the cranial nerves and to the brain. In most cases of closed injury in young persons a good prognosis can be given if the patient survives the first twenty-four hours. The prognosis depends on the severity of the injury and the age, previous personality and intelligence of the patient. A small portion of patients with head injury will be permanently unfit because of physical destruction of brain tissue or cranial nerves, impairment of intellect and memory, traumatic epilepsy, organic complications during convalescence and chronic postconcussional syndrome. Russell advocates early return to work after an injury to the head.

ECHOLS, New Orleans.

DEFECTS OF SMELL AFTER HEAD INJURY. A. D. LEIGH, Lancet **1**:38 (Jan. 9) 1943.

Traumatic impairment of the sense of smell has received relatively little attention until recent years. Ogle described 3 cases of anosmia consequent to injury of the head. He stated that there could be little doubt that this loss was due to rupture of the olfactory nerves as

they pass from the olfactory bulb through the ethmoid bone. Goland (1937) refuted this statement and suggested, in agreement with Legg (1873), that the loss results from damage to the lateral olfactory stria and tip of the temporal lobe by impact against the lesser wing of the sphenoid.

Of 1,000 patients representing consecutive admissions for head injuries to a military hospital, 72 (7.2 per cent) had impairment of the sense of smell. Simple clinical tests were used. The test substances were coffee, camphor, eucalyptol, peppermint and clove. An airway free of blood and mucus was considered satisfactory. A single sniff up each nostril replaced the technic of Elsberg and Levy (1935). Of the 72 patients, 2 had gunshot wounds, 2 died, 41 had complete anosmia, 31 presented general diminution of olfactory acuity or unilateral anosmia and 12 complained of parosmia. In 18 of the patients the injury was occipital (in 12 associated with fracture); in 30, frontal (in 27 associated with fracture), and in 7, parietotemporal, and the site of injury in the remaining 17 patients was not determined although 10 of these had fractures. Five of the occipital fractures had fissures into the foramen magnum, and 14 of the frontal fractures involved the frontal sinus, with rhinorrhea in 5 cases.

The violence of the injury was usually extreme, as shown by the high incidence of organic neurologic signs. The post-traumatic amnesia was reckoned in days for all but 6 patients. Twenty-six men were so incapacited that they were discharged from the Army (36.4 per cent of this group, as compared with 29.6 per cent of the entire group of 1,000 patients). Only 34 men returned to full duty, and 12 were returned as fit for light work only.

In only 6 of the 72 patients has any recovery of smell been noted, the data on these men being as follows:

| Site of Violence | Parosmia | Time of Recovery |
|---|---|---|
| Crush | Yes | 20 days |
| Frontal region | Yes | 3 mo. |
| Occipital region | Yes | 12 mo. |
| Crush | No | 4 mo. |
| Frontal region | No | 3 mo. |
| Occipital region | No | 1 mo. |

Parosmia was observed in 12 patients. Two of these men experienced unpleasant smells spontaneously, and in the remainder the parosmia was associated with olfactory stimulation. The type of smell was nearly always unpleasant. The onset of post-traumatic parosmia was usually delayed from seven days to three months. Of the 6 patients who recovered, 3 experienced a period of parosmia, and the question arises as to whether it is part of the recovery cycle.

In 2 patients loss of taste and loss of smell, with subsequent recovery, went hand in hand. Most patients had no disturbance of taste. Of 41 with complete anosmia, only 6 complained of change in taste. Of the entire group of 72, only 14 complained of disturbance in taste. In 9 of these 14 patients primary tastes were preserved and only appreciation of flavors was lacking. In 2 taste was perverted. Six of the 14 patients had parosmia. The results for this group of patients indicate that the connection between taste and smell is not so close as has been popularly supposed.

The inconsant association of the loss of taste and loss of smell in most cases is not fully explained by the clinical observations. Perhaps taste is more affected by olfactory stimuli in some persons. In addition to the tearing of the olfactory filaments, there may be damage to the temporosphenoid lobe or to the region of the anterior perforated crater. Also, taste fibers may be concomitantly affected in their course through the petrous bones. Seven of the 14 patients with disturbance in taste showed a direct fissured fracture from the parietotemporo-occipital region toward the base and had other signs of possible petrous damage.

SANDERS, Philadelphia.

CHRONIC PARKINSONISM. ARTHUR HALL, Lancet **1**:193 (Feb. 13) 1943.

Hall suggests that the activity of the infective agent of von Economo's encephalitis lethargica does not necessarily cease when the acute stage is over. He points out that symptoms of the chronic stage may remain unchanged for years and then become progressively worse, or entirely new symptoms may appear at any time. Sudden death is by no means rare in the chronic stage, an event suggesting active extension of the poison to a vital center in the brain stem.

Hall points out the variability in the required dose of drugs of the atropine series and indicates that some patients with parkinsonism grow steadily worse while receiving a maximum dose, while the condition of others remains unchanged with little or no treatment.

A study of the progression of hypokinesis in 21 male patients showed that in 12 it was unchanged eight years or more after onset. Of 10 females studied during a corresponding period, the hypokenesis of only 4 remained unchanged.

Interference with locomotion is not so serious when only one of the legs is involved, since the forward-tilted trunk is supported by the unaffected leg. With both legs affected falling forward becomes a hazard. Hall points out that in some patients there is backward extension of the body and that some of these patients exhibit a mincing gait, taking short steps on the toes.

The results of atropine therapy for the tremor, like those of other forms of therapy, are inconstant. The same holds true for the oculogyric crises and for closure of the eyes. Hall cites 150 patients with the oculogyric attacks of parkinsonism, most of whom remain subject to the crises in spite of treatment.

The primary factor in drooling is increased secretion of saliva, but the forward and downward posture of the head and the diminished activity of the swallowing reflex are important. In most cases the atropine drugs do not cause uncomfortable diminution of saliva. If atropine fails, high voltage roentgen therapy over the salivary glands often gives relief. The duration of the effect of roentgen irradiation seems to be limited, so that treatment must be repeated. Roentgen rays may also cause the greasiness of the face to disappear.

SANDERS, Philadelphia.

A WEBER SYNDROME OF SYPHILITIC ORIGIN. ADHERBAL TOLOSA and V. VENTURI, Rev. neurol. e psiquiat. de São Paulo **5**:1, 1939.

This report concerns a case of syphilis in which the neurologic disorder evolved in three phases: (1) almost complete paralysis of the left oculomotor nerve; (2) appearance of right hemiplegia, predominating in the arm, face and tongue, a month later, and (3) slight involvement of the right oculomotor nerve. The eye symptoms appeared during active therapy with an arsenical compound, and the hemiparesis, as a reaction to the inauguration of malarial therapy. The signs disappeared gradually with continued treatment, only slight paresis of the oculomotor nerve persisting. The authors explain the patient's difficulties on the basis of a spreading basilar meningitis of syphilitic origin in the peduncular region.

BAILEY, Chicago.

EPILEPTIC ATTACKS FOLLOWING ELECTRICAL INJURY. DARCY DE MENDONÇA UCHÔA, Arq. assist. psicopat. estad. São Paulo **7**:215 (March-June) 1942.

On Dec. 18, 1940, a white man aged 27, an electrician, was thrown down and rendered unconscious for forty minutes by contact with a strong electric current. He seemed to recover well, but nineteen days later, after he had returned to work, major convulsive seizures began to appear, the frequency of which varied from two a day to three or four a month. No data are given regarding the duration of the attacks or the date of admission to the hospital.

The results of neurologic examination were negative; the blood pressure was 120 systolic and 80 diastolic, and there was no evidence of disease of the internal organs. Roentgenograms of the skull and examinations of the spinal fluid revealed nothing abnormal. The pneumoencephalogram showed mild internal hydrocephalus. There were no mental changes. The personal and family histories were negative for epilepsy.

The author concludes that the electrical trauma was the cause of the convulsive seizures.

SAVITSKY, New York.

## Treatment, Neurosurgery

THE TREATMENT OF INVOLUTIONAL PSYCHOSES WITH DIETHYL STILBESTROL. EUGENE DAVIDOFF, E. C. REIFENSTEIN and GERALD L. GOODSTONE, Am. J. Psychiat. **99**:557 (Jan.) 1943.

Davidoff, Reifenstein and Goodstone report the results of treatment of 60 women with involutional mental disorders by means of large doses of estrogenic substances administered for one to two months. Forty-five of these patients received diethylstilbestrol. The doses employed were sufficient to produce proliferation of the endometrium. Of the total group of 60 women, 37 showed improvement. The best results were obtained in patients with transitory depressed and agitated states associated with the climacterium. The psychotic manifestations of the patients with severe disturbances were not materially affected. Other psychoses occurring incidentally in the involutional period were not affected by the estrogen therapy. The authors conclude that estrogen therapy has a definite value in the therapy of mild involutional psychoses.

FORSTER, Philadelphia.

DISAPPOINTING RESULTS WITH BILATERAL PREFRONTAL LOBOTOMY IN CHRONIC SCHIZOPHRENIA. GERT HEILBRUNN and PAUL HLETKO, Am. J. Psychiat. **99**:569 (Jan.) 1943.

Heilbrunn and Hletko studied 10 patients with schizophrenia and 1 mentally deficient and excited patient all of whom had been subjected to prefrontal lobotomy. At operation the white matter was sectioned as far posteriorly as possible. Two patients died after operation —1 of pneumonia and the other of hemorrhage of the frontal lobe. After a follow-up period of nine months only 2 patients showed improvement, and this was slight. Not only did the mental status of 1 patient become worse, but epileptiform convulsions developed. The authors state that prefrontal lobotomy is not recommended in the therapy of schizophrenia.

FORSTER, Philadelphia.

A COMPARATIVE STUDY OF THE COMBINED METRAZOL-HYPOGLYCEMIC SHOCK TREATMENT AND SPONTANEOUS IMPROVEMENTS IN SCHIZOPHRENIA. J. NOTKIN, L. E. WATTS, G. W. SHANNON, C. E. NILES and F. J. DENATALE, J. Nerv. & Ment. Dis. **97**:62 (Jan.) 1943.

The authors review the literature on the use of the shock treatment of the psychoses by the combined metrazol and hypoglycemia methods. They used insulin to produce hypoglycemia, after four and one-half hours of which the patients were given a convulsive dose of metrazol intravenously. The results of treatment of 100 patients, mostly with chronic disorders, are reported and compared with the incidence of spontaneous recovery in 50 untreated patients. In general the untreated patients had been ill for a shorter time than the treated ones. Thirty-seven per cent of the treated patients improved, but 54 per cent relapsed, while 16 per cent of the untreated patients who recovered had a relapse. The results in both groups were better for men than for women. Of the patients, both those who were treated and those who improved spontaneously, with a shorter duration of the psychosis, a higher percentage showed improvement and longer-lasting remissions. The final improved state of the untreated patients seemed better and more enduring than that of the treated group. Paranoid schizophrenia was the most common psychosis in each group. Paranoid and catatonic patients showed an equal tendency to improvement with treatment, while the condition of the hebephrenic patients improved least. Vertebral fractures occurred in 7 per cent of the treated patients, and 2 men died during prolonged coma. The authors conclude that the combined method of therapy is slightly more effective than the use of insulin alone and decidedly better than metrazol shock alone, especially since the incidence of vertebral fracture is considerably less.

CHODOFF, M. C., A. U. S.

GROUP PSYCHOTHERAPY FOR WAR NEUROSES. DONALD BLAIR, Lancet **1**:204 (Feb. 13) 1943.

To combat the problem of the treatment of neuroses in the armed services, Blair evolved a scheme whereby group treatment could be administered. Therapy was begun on the day of the patient's admission to the hospital by giving him a typewritten form pertinent to encouragement and reassurance. The men who read the forms showed greater improvement in tone and attitude than those who did not. The next day each patient was interviewed and, except for the low grade mental defectives, was told to write a history of his life, with special reference to any events which may have affected his mental welfare. The biographies revealed abundant data of importance in diagnosis and treatment; in addition, nearly all the patients agreed that they found it a great relief to unburden their minds. Most of them felt that they were better able to express their thoughts on paper.

A second interview was held with each patient after the completion of his biography in order to collect further data and to plan future treatment. Most of the patients were found suitable to attend the group psychotherapy lectures, which consisted of a series of about ten lectures of one hour each. The subject matter of each of the ten lectures is given in outline form. By simplification and illustrations it was possible to hold the attention of most of the hearers. Although only a few remembered and understood details, most of them appreciated the general gist and implications of the material. Blair believes that an important factor in the success of the method was the group attendance at lectures. This enabled the patient to realize that his neurotic symptoms were far from peculiar to himself, and, what is most important, every one present felt that he was at last receiving adequate treatment.

The proportion of patients returning to duty after treatment, either in their own units or to a more suitable occupation, has compared favorably with the results obtained by other psychiatrists. No man was discharged from the Army before being ready for civilian work. Blair suggests, in view of the possibility of relapse, that discharged patients should continue attendance at a hospital for rehabilitation and therapy.

SANDERS, Philadelphia.

# Society Transactions

## ILLINOIS PSYCHIATRIC SOCIETY

FRANCIS J. GERTY, M.D., *President, in the Chair*

*Regular Meeting, March 4, 1943*

**Psychiatric Study of a Man Suffering from a Convulsive Disorder.** DR. LEO H. BARTEMEIER.

The patient presented the characteristic manifestations of idiopathic epilepsy, and various examinations failed to reveal organic disease of the central nervous system. The importance of understanding the preconvulsive period and its relation to the later convulsive disorder was emphasized. The study revealed how his mother's overprotective attitude had influenced the whole early mental development of the patient and had seriously interfered with the natural expression of his aggressiveness, which was later forced into a pathologic mode of discharge represented by his attacks. His convulsive disorder was precipitated by two traumatic surgical experiences. The relation between his anxiety and his seizures was demonstrated by several episodes which occurred during the course of the treatment. Although the patient had to continue under medication with phenobarbital, his improvement was greatly enhanced as a result of the psychotherapy.

This paper was published in full in the March 1943 issue of the *Bulletin of the Menninger Clinic*, page 62.

DISCUSSION

DR. CLARENCE A. NEYMANN: Dr. Bartemeier's paper is a brilliant exposition of the psychologic development of the patient from the early anal-erotic period through the period of the Oedipus complex to the present time. I should like to ask Dr. Bartemeier whether there is not some linking at the oral-anal-erotic level between the increase in the attacks and the patient's having stopped smoking at this time. The paper is not just another presentation of an interesting case. The clever analysis is developed with superior technic; more than this, it points the way toward a rational treatment of certain idiopathic forms of epilepsy. These epileptic syndromes will become more common as the tempo of the war increases and therefore will become a challenge to the therapeutic efforts of many physicians and psychiatrists.

For a number of months during the first world war I had charge of a ward of patients with fits. Some had seizures which undoubtedly were due to organic development. Some had had attacks throughout life, beginning in early childhood, with only a temporary lull during the years following puberty. Some had spells which were undoubtedly of hysterical origin, usually closely connected with the psychic strains and stresses of the war. Finally, some patients had seizures which in the strict sense were due neither to idiopathic epilepsy nor to hysteria. At times such seizures simulated hysteria perfectly; at other times they were exactly like a grand mal attack. For want of a better name this disease, or, rather, this loose group of diseases, was called hysteroepilepsy.

My associates and I really had no exact knowledge about any of the patients. Most of them improved after they were assured that they would receive an honorable discharge from the army and be sent back to their homes. The patients with epilepsy of organic and idiopathic origin also improved under a regimen of sedation, rest and psychotherapy.

At this point I should like to ask Dr. Bartemeier what he understands by the terms true, idiopathic or essential epilepsy. In my opinion, this so-called disease is only a syndrome, under which many conditions characterized by seizures are included.

DR. RALPH HAMILL: While I was at the Children's Memorial Hospital I saw a great many children who had petit mal, and I felt sure I could prevent any of these children from having attacks merely by insisting that they try to concentrate on what they were thinking just before the spell began. I asked them to catch themselves and recall what they were thinking at that moment. One child especially, a boy with narcolepsy, had begun to have his attacks just after his mother had died in giving birth to a child, the second in the family, and it was obvious that this episode was much in the front of his mind. While he stood talking to me, he might have five or six spells in which his voice went up, his hand shook a little and his knees became weak, so that I expected him to fall. I saw him frequently for three months. After about a month he ceased to have the spells in my presence. He still had them elsewhere. This was true of a great many of these children.

I recently saw a man who was in the armed services. He consulted me because he could not concentrate as he studied the lessons in training. He could not control his attention. As he talked to me, he seemed bright, alert and responsive; then when I began to talk to him, I soon saw his upper eyelids drop a trifle. At this moment he seemed to be having a petit mal attack. With it would come and go in his eyes as violent anger as I have ever seen in any one's eyes. The anger would come when I spoke a little more sharply or insisted a little more definitely on his giving me attention—anything that interfered with his running of himself. I have seen a good many such patients whom I felt were on the borderline between an epileptic and a nonepileptic state—between the possession of the ability to place attention at will and the failure of such ability. The ability to place and keep placed the attention I think of as a higher quality of consciousness. It is to be understood in somewhat the same way as Lennox considers the epileptic phenomenon when he draws the diagram of a pool that has a high bank on one side and a low bank on the other. The pool is filled with hereditary and emotional considerations, and then something is spilled into the pool and it overflows. This is the epileptic attack. For about three years I had as a patient a girl who began to have epileptic attacks at the age of 17 months. I saw her during a seizure in my clinic room when she was about 14 years old. I carried her into the examining room while she was still in convulsions. The father followed. As she passed through the tonic and clonic convulsive phases and began to come to, she lifted her head and saw her father, and I have never seen such horror on any person's face as on that child's face for a moment. What was going on in her mind, of course, I do not know. I saw her over a period of about three years, and every time she came to my clinic, which was twice or three times a week, she would draw pictures. She drew pictures that revealed some battle going on in her mind, a struggle which had to do with things that were acceptable and things that were not acceptable. One of the principal things that she drew was a fireman; the figure of the fireman was always much like the male genitals, and from it would come a stream onto a building on fire. Down to this figure the first time she drew it came the stem from a round thing she called "a sucker." When I asked her about this, she was fussed for a moment and then said: "I'll draw you something good," and then drew a milk wagon. At the same time she was drawing a table with a broom on one side and a shovel on the other. These were the street sweeper's implements. Once she drew them on top of the table; that was what one had to eat on the table. The table was something one had to keep one's hands off—something all have to learn in childhood. At the same time, she was saying that she had to keep her hands off her genitals. The table and the genitals were interchangeable. This led to confusion. The convulsive attack is decisive; something of importance happens. The epileptic attack is the decision led up to by the confusion.

Dr. T. M. French: Dr. Bartemeier's paper is simple and direct and brings out some of the important events in the patient's life in clear relation to the symptoms.

I should like to ask Dr. Bartemeier a question. The patient's material brings out some psychologic reactions with a directness that impresses me as somewhat unusual. Is this undistorted nature of the material characteristic of patients with convulsive disorders, as it is of some psychotic patients, or is there another explanation?

Dr. Leo H. Bartemeier: In answer to Dr. Neymann's question, I am not aware of any oral or anal connection between the patient's stopping his smoking and the occurrence of his attacks. The article which he had read aroused his anxiety, and he stopped smoking out of fright. The shower of petit mal attacks represented unconsciously motivated attempts to relieve this anxiety. Dr. Neymann also asked what I understand by true, idiopathic or essential epilepsy. I dislike these terms as thoroughly as does Dr. Wheeler, but I have used them to make it clear that this patient was one whom my colleagues regarded as suffering from genuine epilepsy, not one whose attacks were the manifestations of hysteria. The more carefully one studies the lives of epileptic persons, the more one may come to see that their seizures have meaning and significance in their psychic economy. The patient whose illness I have described not only bit his tongue severely on numerous occasions but fell off his bed several times and hurt himself during his attacks. Such attacks represent the type of epilepsy which the average neuropsychiatrist would call idiopathic epilepsy, for lack of sufficiently thorough psychiatric investigation.

The directness of the material about which Dr. French inquired becomes understandable when one realizes that the samples of material which followed one another so closely in the presentation were obtained at infrequent intervals over a period of three years.

The psychiatric study of these patients requires much more careful and painstaking investigation than is necessary with the average patient who suffers from a neurosis. One must be persistent and cautious in one's conclusions. In this connection, I am reminded of a

youth who had always had good health until four weeks after his tonsillectomy, at the age of 19 years, when he experienced his first grand mal seizures. Although one would be inclined to associate his surgical experience and the onset of his disorder, it was not until his fifteenth visit that I discovered that just prior to his tonsillectomy his closest friend, the only person he had ever really loved, had died of rapidly fatal pneumonia. His wife remarked: "John has never gotten over it. He talks about Bill all the time. He dreams about him, and he mentions his name when he comes out of his spells."

I cite this material to point out the necessity of one's uncovering the psychologic factors involved in the production of convulsive disorders. Much more could be learned about the seizures in many cases if the etiologic factors were searched for more diligently. Too great reliance has been placed on the efficacy of chemical therapy alone in attempting to bring relief to such sufferers.

**Hysteria, with Symptoms Referable to War Experience: Report of a Case.** DR. BORIS S. URY.

A white man aged 50 was referred to the psychiatric dispensary of the Illinois Neuropsychiatric Institute in September 1942. The presenting symptoms were those of intense pain in the legs and neck and inability to walk. Because of this pain, he had been unable to lie down or to sleep in a normal position, and he had been hospitalized for three months previously at a veterans' hospital. There complete study revealed no organic abnormality which could account for the symptoms, and the condition was diagnosed as psychoneurosis, hysterical type.

The patient was a veteran of the first world war, and it later became apparent that one of the determining factors in his illness was an unresolved affect relating to his war experiences. The initial examination of the patient was conducted under difficulties, since he held his limbs under such muscular tension that any passive movement of them by the examiner caused him to cry out with intense pain. However, by constant suggestion, the patient gradually became able to relax so that a neurologic examination could be made. This study revealed no organic defect.

Discussion of the patient's life situation revealed that many of his anxieties centered about the fact that his eldest son was soon to be drafted. The depth of these anxieties seemed to be related to the patient's own combat experiences, and, when he was asked whether his own memories of the war had disturbed him, he answered significantly, "Doctor, have you ever seen men crazed with fear?" In order to determine the treatability of the patient in the shortest possible time, it was decided to hospitalize him and to conduct explorations while he was under narcosis induced by sodium amytal, a procedure which usually permits the revealing of psychodynamic factors in less time than is consumed by the usual free association interviews.

During the initial exploration these hopes were fulfilled beyond expectation. The patient poured out an intense and affectively charged recital of his war and combat experiences. Among the events which he described was the incident of his having bayoneted a German soldier through the neck in hand-to-hand combat. The patient still manifested considerable guilt in relation to these experiences and seemed to abreact with extreme intensity to many disturbing and terrorizing memories. During the exploration the patient clung to the therapeutist's hand with almost childlike dependence. The therapeutist did not remain passive throughout this recital but interpreted the material to the patient, pointing out that it was the anxiety relating to these experiences which had been transformed into somatic tensions and pain. The patient remained disturbed for a considerable time after the end of the exploration and finally had to have additional sedation.

Much improvement was noted the day after the first exploration. The patient had lost many of his symptoms, used his legs in a limited fashion and was able to resume sleeping in a normal position. In two successive explorations with the use of amytal narcosis the initial experience was amplified and repeated, with the result that after the third treatment the patient was free from symptoms in the somatic sphere. The more usual psychotherapeutic interviews were then instituted, the patient making free associations while in the reclining position. Material obtained in these interviews was of two categories: (1) additional affective abreactions and recollections of material referable to the war experiences and (2) material relating to the patient's character development and life situation. As the totality of the syndrome was revealed, it was seen that the second category was of at least equal etiologic importance with the war material. Indicative of the patient's reaction to his combat experiences was the fact that he recalled a scene with an affective response equal to that which was obtained when he was under amytal narcosis. The patient reconstructed in detail a scene in which a bridge which he had been helping to construct under fire was struck by an enemy shell and he and his companions were killed or thrown into the water. When this recital reached its climax, the patient recreated all the symptoms which he had manifested on

admission—i. e., extreme tension and pain in the neck and legs, flexion of the entire body and inability to perform voluntary muscular movements. In about ten treatment sessions these war memories were gradually exhausted and abreacted, and the patient began to reveal material relating to his personality development and life situation. The latter indicated that the patient's personality had been molded to that of an intensely masochistic character, to which, however, he had been able to make a satisfactory adjustment until the cumulative effect of many anxieties had precipitated the present illness.

The patient's early life history was one of extreme deprivation. The father had been killed in an accident by an electric current, when, curiously, his legs had been severely traumatized. Because of the father's death, the patient and his family were dependent on charity resources, which were often inadequate to meet their simplest needs, such as food and clothing. The two adults who were closest to the patient in his formative years—his mother and his aunt, who later cared for him—were victims of extremely disabling somatic diseases. The patient was greatly impressed by the suffering of these two women. He became very conscientious and assumed many family responsibilities not directly related to his own situation. This resulted in much imposition. Nevertheless, he made a good adjustment in adult life, was later drafted and returned from the war without any overt physical or psychiatric symptoms. He had an excellent military record, was twice wounded in action and returned with the rank of sergeant.

After his return he married, had 3 children and made a good adjustment for the first ten years, after which he experienced a series of financial reverses and loss of employment status. The patient had been a lineman for the telephone company and was now demoted to the position of janitor. Because of this demotion, he was unable to meet his financial obligations and was greatly in debt. He began to equate the residue of anxiety resulting from his war experiences with the humiliations that were engendered by his life situation. In one of the treatment interviews he stated: "When I began to think about these worries, I thought maybe it would have been better if I had been killed in the war." While brooding over the deprivations in his economic and employment status, the patient was overcome by fits of weeping, which at times cumulated in an ineffectual and impotent rage. The latter feelings may have catalyzed the memory of his more successful aggressive experiences.

The patient also manifested an intense fear that if his son entered the Army he would be killed. Because of this fear, he continually insisted that the son join either the Marines or the Navy. Gradually it became apparent that the patient's intense fear for the safety of his son was a projection of his own guilt in reference to the killing of the German soldier. He had assumed an "eye for an eye" attitude, feeling that because of his own aggression the son would be killed in return. As the psychiatrist interpreted these possibilities, the patient agreed that he had actually had such fears and was gradually able to master these anxieties as their unrealistic nature was indicated to him.

The patient remained in the hospital until December 1942, at which time he was discharged free from symptoms. He has now returned to his former employment and consults the psychiatrist bimonthly for supportive therapy.

This patient's neurosis, although rooted in character development, seemed more a reaction to threats arising from the external environment and appeared not to be much influenced by the more usual psychosexual problems, which were once considered the ubiquitous cause of every neurotic illness.

### DISCUSSION

DR. G. A. WILSON: The temptation is great to think of and to discuss this case in connection with the traumatic neuroses of war, but it must be remembered that the symptoms did not present themselves until nearly twenty-five years after the traumatic war experiences to which the patient abreacts. It must also be remembered that amytal does not release unconscious material, but only frees preconscious material.

That the symptoms occurred in a situation in which the patient's sons were about to expose themselves to experiences that might be similar to those undergone by the patient in the last world war is probably of great significance, but certainly not the paramount reason for the precipitation of the present neurotic picture.

In my opinion this case is an extremely interesting instance of conversion hysteria. The presentation is correctly titled, but I question the validity of the last sentence. Therefore discussion of the case must follow the lines of present knowledge concerning conversion hysteria. I shall confine myself to a brief résumé of this body of knowledge and shall mention only inferentially the case material presented. There are several reasons for such a restriction: First, the time is limited, and, second, the unconscious material is insufficient to warrant an attempt at reconstruction of the dynamics of the symptoms. The sexual history has either

been suppressed (not confessed) or has undergone repression. No dreams are reported out of the present, the immediate past or the early developmental period.

Conversion hysteria, with particular reference to the symptoms relating to the autonomic vegetative system, has long been a subject for investigation and research. Valuable contributions have been made by numerous investigators. Freud first discussed, and Abraham and Ferenczi further elaborated, the theory of organ erogenity, or, to use Ferenczi's term, "genitalization of organs." By this term he meant that an organ could assume a genital significance for the person who was predisposed to hysterical symptoms, and he stated specifically that all hysterical symptoms contain a repressed, conscience-forbidden sexual impulse. Ferenczi stated that "hysteria could imitate any disease." Psychoanalysis has shown that before the child reaches the genital stage, he must pass through oral and anal stages in libido development, and there is evidence to lead one to believe that hysterias are characterized by regressions to these stages. Actually, however, the hysterias do not abandon the sexual, or, better, the phallic, stage of sexual organization, or the genital relation to fantasied objects, but this fantasied relation is translated, as it were, into pregenital language. The pregenital fixations determine only the point at which the pregenital process will find expression. The term "fantasied objects" refers to the withdrawal of the libido from actual object choice and the substitution of fantasy. This represents a regression from normal development back to an earlier stage of organization, when fantasy constituted the principal source of satisfaction.

Therefore one must take into consideration the phenomenon of regression. Every disappointment in life tends to precipitate a regression to an earlier phase of gratification. Disappointment or frustration in adult sexual expression tends to reactivate infantile forms of satisfaction. The character of the infantile sexuality which will play the leading role in the regression depends on the person's particular point or points of fixation. But in hysteria the phallic phase particularly occupies the attention. (In a previously published paper I demonstrated this distinction in contrasting conversion hysteria with what is commonly termed "organ neurosis.") Since the predisposing elements of any neurosis occur in early childhood, it is necessary to analyze in detail these determinants in order to arrive at any conclusions. Every hysterical symptom represents an attempt at sexual gratification in a distorted or symbolic manner, and since every hysterical symptom is also a somatic phenomenon, or, to express it differently, since every affect, normal or abnormal, must ultimately be expressed in some physical way, the possibility of an aim-inhibited or aim-displaced expression in an organ becomes comprehensible. The leap from psychic to physical is called conversion.

The prerequisite for the development of a conversion symptom is, first, the turning from reality to fantasy, a process made necessary by the repression of the constellation, which is referred to as the Oedipus complex. The repression or failure of a solution of the Oedipus complex often results in what may be called introversion, i. e., the turning inward onto the self of the libido and the substitution of fantasied infantile sexual objects for real sexual objects. Hence, the symptom represents an autoplastic attempt at solution of a sexual conflict. Because of this introversion, hysterical persons appear to be almost completely "turned inward," and their symptoms present not outwardly directed activities but internal innervation, affecting their own bodies. Psychoanalytic investigation has shown that a motor paralysis represents a defense against an action (at the deepest level; an infantile sexual action) and that a muscle spasm represents an outburst of affect uncontrolled by the ego. So it appears that in all instances conversion symptoms represent a cathexis of offensive, usually destructive, conscience-forbidden impulses concentrated on the construction of a symptom. This is accomplished through the process of condensation (similar to the mechanism of the dream) and utilizes symbolic representation.

Hysterical symptoms may appear in any part of the body. What determines the part of the body chosen? It may be assumed that the symptom represents for the most part the solution of a sexual conflict according to the libido development of the patient.

Identification may play a prominent role in the choice of a conversion symptom, often an identification with a parent or sibling. This fact may lead to the mistake of one's attributing the frequency of similar familial organic lesions to hereditary factors.

The circumstances which determine the site of a conversion symptom are: (1) somatic compliance (constitutional predisposition); (2) special factors in relation to the infantile history of the patient; (3) a partial pregenital fixation, and (4) the symbolic suitability for the conversion.

If one applies, rather loosely, I must admit, the four principles outlined as determinants for conversion symptoms, one finds that the patient whose case is under discussion was apparently a weak, undernourished child; a sister is in a hospital with a cerebral lesion; a brother is alcoholic, and the mother and an aunt suffered from severe, incapacitating physical illnesses; one may assume, therefore, the presence of both constitutional and strong environmental influences. One may assume considerable significance for certain details in the

infantile history which may be considered to have had a "traumatic" effect on this man's development. Probably the most important detail about which there is any knowledge is the trauma experienced by the patient when his father died. This occurred at a time when the patient was at the peak of his Oedipus conflict. The very nature of the cause of the father's death must have influenced and complicated the patient's "failure of resolution" of this conflict.

The history reveals nothing with respect to actual sexual traumas which may have occurred, and probably did. Also, the history tells little about the third prerequisite, pregenital fixation, but there is known to have been a strong fixation to the mother, which after her death was transferred to the aunt.

The fourth category, the symbolic suitability for conversion, of necessity includes mechanisms similar to those observed in dream organization—i. e., distortion, condensation, projection, identification, displacement and, as indicated, symbolism.

One could indulge in considerable speculation, but it is enough merely to call attention to the following facts as related to this case: The patient was "pigeon toed" and experienced considerable humiliation as a result of this defect. The father suffered a severe accident to his legs, and the accident resulted in death. The mother's cardiac condition resulted in severe swelling of her legs, and the patient was permitted, and apparently encouraged, to massage them at a time when he was already under considerable emotional strain, for reasons previously stated. Certainly, the mother's legs must have been extremely painful, and it is probable that she experienced pain referred to the chest with difficulty in breathing. It is interesting, and probably significant, that the patient, who suffered from an extreme sense of guilt, which he attempted to displace onto his war experience, asked himself a question which was almost identical with that expressed by the mother during her illness.

It is my opinion that this "sense of guilt" was actually related to destructive impulses which underwent repression during the period of childhood development and which found expression in his war experience, were again repressed and at the onset of his illness were taking the form of unconscious or preconscious fantasy. There is considerable evidence to justify this conclusion. For example, the hostile, destructive impulses did break through with hostile feelings toward his wife, the conscious hostility, which was well rationalized, toward his employment superiors, and the fantasies regarding his sons which he attempted to master by a "reaction formation" of solicitude for their welfare.

What precipitated this illness? Probably the real cause has not yet appeared in the verbalized material. Only the superficial determinants are evident—a gradual, but severe, decline in his financial status; his sons' imminent departure from the family unit into a situation of danger similar to that which he previously experienced, and, last, but probably of greatest importance, the fact that just as he was pushed downward from a position of relative importance to one of unimportance in the telephone company, he also faced his being pushed out of the role of a hero in the last war to one of little importance in this war, as well as the relinquishment in favor of his vigorous and ambitious sons of the attention and glamour attendant on his past masculine attainments.

Dr. Boris Ury: Dr. Wilson has attempted to fit this hysterical syndrome into the framework of the classic freudian psychodynamics; that is, he has frankly stated that every hysteria is sexual in its dynamic causation. Such an attempt brings to the fore the problem of how much material in the total personality can be designated as sexual in origin and meaning. When hysterical neuroses were first studied by Freud, the sexual impulses and their transformations were a guide to the complexity offered both by the symptoms and by the personality of the patient. Obviously, the reason was that the first neuroses so studied were predominantly disorders in the integration and expression of the libido. Then, as each level of the personality organization was discovered, the material was described in sexual or libidinal terms.

At present, there has accumulated a tremendous amount of material relating to the dynamic development of the personality, and more specifically to the development of the effective ego. It is questionable whether all this material can be described in sexual or libidinal terms without violence both to the material and to the original implication of these terms. Kardiner (Traumatic Neuroses of War, Psychosomatic Medicine Monographs II-III, National Research Council, New York, Paul B. Hoeber, Inc., 1941) has pointed out that there are many ego functions the task of which is not so much the adjustment and maturation of libidinal strivings as the mastery of the external world.

I am inclined to believe that it is the latter functions of the ego which have broken down in the case presented. I believe it is a mistake to equate the total personality with those aspects of the ego which have to do with the modification and expression of libidinal drives. I believe that the aspects which have to do with the mastery of the external world are related to the total character, which is in this case a masochistic one, but their disorganization need not imply a primarily sexual dynamic process.

## NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND NEW YORK NEUROLOGICAL SOCIETY

GEORGE A. BLAKESLEE, M.D., *President, New York Neurological Society, Presiding*

*Joint Meeting, March 9, 1943*

**Results of Electric Therapy of Facial Spasm and of Paralysis of the Vocal Cords.** DR. CHARLES O. FIERTZ (by invitation).

My purpose in this paper is to emphasize the value of rational electric therapy and the validity of the biologic concepts developed during the past century, since the introduction of electricity into neurology by Duchenne de Boulogne in 1845. Regardless of the many theories concerning the biochemical, histochemical, biophysical and other aspects of the possible mode of action of the electric current on the living organism, one set of facts is beyond controversy: the observations of Duchenne, Remak, de Watteville and others, finally formulated by Dejerine; the stimulating effect of the steady cathode on the regeneration of injured nerve tissue; the sedative and soothing effect of the steady anode on spasms in the musculature, and the value of stimulation of individual muscles in treatment of lesions of peripheral nerves.

The results achieved by the rational application of these principles are shown in two series of cases of generally considered hopeless conditions: postparalytic facial spasm and paralysis of the vocal cords.

The first 4 cases are those of Bell's palsy of from five to twenty-five years' duration before institution of treatment. In all cases there is good or excellent function, and the spasticity—usually more disfiguring than the original paralysis—has disappeared (in 1 case, that of a girl, a dimple has been restored after having been obliterated for many years).

The second series consists of 2 cases of paralysis of the vocal cords—in 1 following thyroidectomy; in the other of obscure origin. In both instances the prognosis as to restoration of voice was poor; both patients talk well today. In the first case the last treatment was given in 1940. In the other the patient has been talking normally for four months. The treatment is the same as that for any other lesion of the peripheral nerves: application of the cathode to the nerve on the side involved (usually over the scar at the lower border of the larynx) and stimulation of the vocal cords themselves with the motor point placed exteriorly directly on the Adam's apple on the side involved. Ordinary electrodes for tests of nerve or muscle function are used, and the contraction of the cord is produced fifty to seventy-five times at a session. A detailed statistical report of my results is found in the article by Weeks and Hinton (Extralaryngeal Division of the Recurrent Laryngeal Nerve, *Ann. Surg.* **116**:251 [Aug.] 1942).

A plea is made for a renewed interest on the part of neurologists in the treatment of patients with injuries of the peripheral nerves, the fate of whom should not be left in the hands of physical therapeutists, whose neurologic knowledge is frequently insufficient.

**Psychic Determinism of Holmes and Freud.** DR. C. P. OBERNDORF.

The name of Oliver Wendell Holmes does not appear in books on early American psychiatry. He was not a psychiatrist according to the concepts of his time, which regarded the mentally ill as doomed from birth. Holmes's essays and novels reveal the medical and sociologic, the philosophic and creative phases of the psychiatrist's scope.

At first glance, it may appear odd to couple Holmes and Freud as interpreters of human behavior. Yet as observers and recorders of the psychopathology of the unconscious and in their understanding of the deterministic effect of the sense of guilt on human conduct, these two diversified men of genius arrived at similar interpretations.

Holmes's background furnishes some clues to his interest in determinism. His father was a Calvinist minister, and the Calvinistic theory was an ever present restriction to the freedom of thought of young Holmes. His medical experiences convinced him that moral obliquities and mental disorders existed for which the person was not responsible. In his essays and novels there are numerous descriptions of the processes which Freud later formulated into a theory and therapeutic method called psychoanalysis. In his three psychiatric novels, "Elsie Venner," "The Guardian Angel" and "A Mortal Antipathy," early determinants are held responsible for the psychopathologic manifestations in the principal characters. His philosophic and psychologic thinking and social conscience led him to believe that society must be rid "of chattel sin and all its logical consequences," which so restricted social custom, warped morality and blocked learning. Later he expressed the conviction that early impressions

determine and dominate the character, even though no traceable pathologic process can be shown in the brain.

Freud was born about fifty years after the birth of Holmes. No curse of age-old ancestral sin hovered over him, nor was he oppressed by any harsh theologic doctrines; yet he did regard his race as a factor which ostracized him socially—especially in his university days. This, however, did not throw him into moody despondency, but it led to his isolation.

A man with exceptional endowments, he could not long remain content in the exactitude and precision of anatomic and physiologic research. His observations on the importance of repressed early memories in the causation of hysterical conditions led him into the field of psychologic medicine and to a new concept of psychic determinism which he conceived of as unconscious and dependent on memories, incidents and impressions originating in earliest childhood, usually with a sexual connotation.

Freud's theory of psychic determinism does not ignore human values and carries with it moral and social implications of previous forms of theologic determinism involving the freedom of the will, against which Holmes protested so effectively. However, it takes this problem away from an irrevocable domination of the past or from an unavoidable damnation in the present and the future unless one has been chosen for redemption. Determinism in all its manifestations, especially as it affects neurotic and mental diseases, now becomes amenable to intervention, and the effects of psychic determinism are opened to change.

The philosophy of psychic determinism is individualistic and for this reason would powerfully affect the attitudes to be expected in social customs and criminal law in their estimation of responsibility in individual conduct. In this respect psychic determinism would invite new social and moral approaches, comparable to those revolutionary changes which followed the overthrow of the doctrine of preordination in Holmes's time.

### DISCUSSION

DR. LELAND E. HINSIE: Progress is the outcome of many forces. What the public finally accepts as an instrument for its betterment is the result not alone of the instrument in question but of the receptivity of the public. I believe that Dr. Oberndorf's communication illustrates the preparation of the medical profession and the lay public for the acceptance of the psychoanalysis of Freud. Dr. Oberndorf is fully aware that he could have cited from the works of others to show that much had gone on before Freud that served to crystallize freudian concepts.

It is not merely of academic interest to trace the history of psychiatry back to ancient times. Historical evaluation broadens one's vision, makes one a better humanitarian, gives a base line for comparisons and adds to the judgment of the value of a given contribution. Or, as Whitwell put it (Historical Notes on Psychiatry, London, H. K. Lewis & Co., Inc., 1936): "It is, indeed, almost possible to say that the attitude of the community to mental disorder is a true indication of the degree of real civilization attained by that community."

To me the value of Dr. Oberndorf's paper lies in the consideration that the body of facts known today as psychoanalysis is the outgrowth of a slowly evolving past reaching back to distant forefathers. Psychiatry was first in the hands of the priests; exorcism was then the keynote of therapy. Even today in certain localities exorcism is a common method of handling the mentally sick person. Haslund (Men and Gods in Mongolia, New York, E. P. Dutton & Co., Inc., 1935) stated that in Mongolia insanity is the result of demoniacal possession. In Malaya the bezoar stone has high value for the treatment of mental disorders. In the Landes district of France, crosses of St. John's-wort are hung over the doors of peasants to keep evil spirits away.

In the course of the early centuries of civilization the priest was gradually replaced by the priest-physician. In this transitional period, covering many centuries, appeared a legion of eminent names—Pythagoras, Alcmaeon, Anaxagoras, Hippocrates, Aristotle, Celsus and Juvenal, to mention but a few. It was in this era of medical evolution that the thought grew slowly that the ills of mankind, or, more specifically, disease and disorder of the individual, could be traced to the man himself, rather than to good and bad gods. Celsus (25 B. C. to A. D. 50) wrote that "if a person has cause for distress, and shows no feeling of that kind, it is a sign that his mind is in an unstable condition." The statement at the time was not without heretic implication, although Hippocrates (460 to 375 B. C.), for example, taught that epilepsy was not a sacred disease.

Down through the centuries man's body became the ever growing object of interest. Theophilus (610 to 641 A. D.) sought the soul by means of dissection; Avicenna (980 to 1037 A. D.) wrote on instinct, memory, imagination and understanding; Rogerius (1180 A. D.) trephined for relief of mania and melancholia, as did Arnoldus de Villa Nova, in 1245; Savonarola (1462) recommended baths for melancholia, and Vesalius (1514 to 1564 A. D.)

laid the foundation for knowledge of cerebral anatomy. The Middle Ages were not prolific; yet the trend was upward.

The third period saw the gradual transition from priest-physician to physician. The mind became the object of scientific study. Investigators were freer now to look into man himself for possible causes of mental deviations. No longer was it considered that man's disposition, his likes and dislikes, his faults and virtues, his stability and instability, were due to the stealthy invasion of good and bad gods into his body. Maybe one ought to be held responsible for some of one's actions, thoughts and feelings. Thus, there came about the theory of psychic determinism, invested with the idea that one's own mind (and all that goes into its origin and development) determined one's conduct. The era of blaming the other fellow, that is, the era of projection, was about to close. Man was at last beginning to get some insight into himself.

Oliver Wendell Holmes (1809 to 1894) helped greatly to foster this new insight. He shook off the rigid Calvinism of his time and established disbelief in the dogma of original sin, miserable slavery and predestination. The acceptance of his concepts was facilitated by the spirit of the time, which saw other rebellious movements of the masses. Abolition of slavery, Darwinism, temperance, women's rights—these, and other popular movements set the stage for a reevaluation of man.

In his three novels—"Elsie Venner," "The Guardian Angel" and "A Mortal Antipathy"—Holmes brought his earlier tendencies into focus. These stories concerned human wrecks, made miserable through their own personal experiences, not by divine decree or preordination. Holmes's approach was a psychodynamic one, in principle not unlike that of Freud, who was to present his formulations about a half-century after Holmes.

Now, today, one can look back on approximately a half-century of research into the influence of the psyche on human conduct; one can measure to a reasonable extent the effects of interpersonal relationships. Concepts of psychoanalysis comprise a new and invaluable tool with which to survey and to correct those faults of human nature that seem to stem from the incorrect growth of the emotions.

I am thankful to Dr. Oberndorf for this opportunity to participate in a discussion of the topic that he has brought to light for members of the society—the contributions of Holmes to psychiatry.

DR. IAGO GALDSTON (by invitation): I have had the pleasure of reading and now of hearing Dr. Oberndorf's paper. It seemed to me that he had cast forth a handful of mercury and it had run into many bright and scintillating globules of thought. He has touched on so many interesting subjects that I am embarrassed in deciding which to discuss. Following my own bias, I select two of the many items—Holmes and psychic determinism.

All are beholden to Dr. Oberndorf for his enthusiastic devotion to Holmes. Holmes is, without doubt, one of the major personalities in the American literary and scientific heritage. I must, however, confess that the coupling of Holmes and Freud seems to me somewhat specious. One can couple the seal with the elephant, for both are mammals and both enjoy the water; yet what a vast difference there is between them.

This is not to deny to Holmes the psychologic insight which Dr. Oberndorf claims for him; it is rather to maintain that psychologic insight does not make a psychiatrist, and that the comparison of a good poet and fair novelist with one of the greatest intellects of the age must inevitably prove a bit startling.

In this connection I can see an interesting problem for Dr. Oberndorf's enthusiastic labors. It would be interesting to know precisely what prompted Holmes to write his novels. Do they constitute "the second part of his Faust"? Dr. Oberndorf might consider a psychobiography of Holmes.

In psychic determinism one is confronted with an interesting paradox. Part of the paradox arises from the undifferentiated use of the terms "predestination" and "psychic determinism." Predestination is primarily a theologic term and in the Calvinistic usage means "the action of God in foreordaining certain of mankind through grace to salvation or eternal life." One needs, also, to recognize that predestination, as formulated by Luther and by Calvin, was a protest to the prevailing Catholic idea of redemption through good deeds and contrition. Only in a secondary sense does predestination mean the predetermination of the fate of men.

Psychic determinism, on the other hand, means the full operation of the laws of causality in the realm of psychology and psychiatry. Psychic determinism is an exclusionist term, which serves to disbar from psychiatry the concept of free will.

Dr. Brill, and before him Dr. Bleuler, have dealt amply with this question. Now, in that connection it is interesting that Holmes, who was nurtured in the Calvinistic tradition, rejected Calvinism in his mature years and became a staunch Unitarian. Yet with his "psychologic insight" he espoused psychic determinism, which in many ways parallels Calvinistic

predeterminism, the significant difference being that omnipotence is vested by the one in God and by the other in Nature. Of course there is still another differences, for whereas God is considered to be an arbitrary ruler, Nature is thought to operate through immutable laws. The psychiatrists, on the other hand, profess "psychic determinism"; yet in their therapeutic practices they operate on the basis of volitionalism. It is a basic dictum in psychiatry that nothing (psychiatrically) can be done for or with a patient save as the patient wills that it be done. The patient is encouraged to cooperate with the therapeutist. He is told not to withhold anything. In other words, the therapy is conducted in an atmosphere of volitionalism and optionalism.

It is of course my intention only to point to these paradoxes—not to attempt their resolution. But these paradoxes are implied and expressed in Dr. Oberndorf's paper and are really of tremendous importance to psychiatric theory and practice. They are worthy of the most earnest study. For bringing them to the fore again—and for a bright and interesting paper—all, I am sure, are thankful to Dr. Oberndorf.

DR. RICHARD BRICKNER: I enjoyed this paper so much that when it ended, and I was prompted to say something in criticism of part of it, I hesitated before doing so. One feature of the paper might be touched on in passing: I missed any reference to evolution, and it ought to be there, for it constituted a great part of what was going on at the time. But I am moved to say a word further. I understand Dr. Oberndorf to say that no plan and no thought-out movement on the part of psychiatrists would have any bearing on the future of aggression as manifested in mass form. I cannot see how a person who knows psychiatry, loves it, has vast experience in it, believes in it thoroughly and practices it successfully and "according to plan" with patients, can make the statement that psychiatrists should retire from the scene when more than one person is concerned. I think that if those of us who say we understand human beings and their behavior—we neurologists and psychiatrists—do not feel we have any contribution to make to a situation like that of today, we had better start all over again.

DR. CLARENCE P. OBERNDORF: I want to thank the speakers, Dr. Hinsie and Dr. Galdston, for their extremely kind handling of the topic. The questions brought up by Dr. Galdston are a bit controversial, and possibly a matter of opinion. It may be interesting to remember in connection with Dr. Hinsie's comment about demons in the body that two remedies of this nature familiar to all still exist. In the old days physicians gave the patient foul-smelling and foul-tasting concoctions—such as the hearts of frogs and the entrails of turtles—to force out the evil spirits by virtue of the nauseating effect. The remedies valerian and asafetida are reminiscent of this early aim and are still in use today.

I feel that Dr. Brickner misheard me, for I had in mind the exact opposite. The last sentence in my paper reads: "It is therefore likely that when long-repressed mass sadism, now flagrantly released in wanton practices of warfare, reaches its point of satiation, society will again revert, in the pattern of Holmes and Freud, to the consideration and respect of the individual's needs as determined by his own experiences." Indeed, it is in the discoveries of the psychiatrists that I think a hope for the future of the world exists; that is, when psychiatrists find methods by which these repressed feelings may be absorbed or are able to direct society in how to handle them easily and without too great a clash with culture, possibly war will no longer occur.

**A Theory of the Neural Mechanism of Stuttering.** DR. SAMUEL T. ORTON.

The emotional factor in stammering and stuttering is self evident, but it must work through some specific neural mechanism to produce the characteristic syndrome. That mechanism is not adequately explained by generalizations concerning such factors as inhibition. "Neurotic" factors are also practically always present in adults, but the question whether they are primary or secondary may be raised. Evidence from observations on children and a case in which onset occurred at the age of 40 are presented. To be acceptable, a theory must explain the hereditary data and the preponderance of males over females. Parakinesias and motor overflow are not limited to the muscles of the peripheral speech mechanism, a fact evidenced in the knee jerk. The relation of the condition to the handedness of the patient and to the family stock is considered. The theory of absence of clearcut unilateral cerebral dominance is offered.

DISCUSSION

DR. I. S. WECHSLER: As I listened to Dr. Orton's paper, it became clear that his is a strictly neurologic approach to the problem of stuttering. Most psychiatrists believe either that stuttering is altogether a neurosis or that a large neurotic element enters into every case of stuttering and stammering. One may concede that imitation, fear, shame, anger, repressed hostility, aggression and narcissism all enter into the neurotic makeup of the

stutterer. None the less, it seems to me that Dr. Orton is right in trying to put more emphasis on structural neurologic concepts. Incidentally, stuttering presents a good problem in psychosomatic medicine: not the armchair type of psychosomatic medicine, which spins theories out of cobwebs, but that which seeks to bridge structure and function by means of chemistry, pharmacology, physiology and anatomy.

Stuttering, as I see it, is a disturbance of both language and articulatory speech. The differentiation between the two, though important, is sometimes overlooked. Speech involves a neural mechanism, which is influenced through numerous pathways from various subcortical structures. The cerebellar component of speech is rarely stressed, nor is the striatal or the thalamic element. One may speak of rigidity or spasticity in articulatory speech; there certainly is an ataxic speech. Indeed, in a variety of organic diseases one may observe speech disorders comparable to stuttering. In cases of Parkinson's syndrome, for instance, one may observe "festination of speech." The same holds for other diseases in which speech anomalies bear resemblance to stammering. Awareness of these facts is the reason that so much attention is paid by teachers of speech to breathing and articulation. It is clear, therefore, that derangement of the articulatory mechanism is one problem in stuttering, while disturbance of language or of symbolic and conceptual thinking is quite another. I take it that Dr. Orton has addressed himself in the main to the disorder of language.

Language, obviously, involves cortical activity of language centers and of association pathways. All these can be colored by emotional disturbances, and there is no doubt that in stammering emotional factors do enter. But I understand why Dr. Orton stresses the facts of cerebral dominance and of both normal and abnormal structural differences. If stammering is a pure neurosis, a so-called emotionally conditioned functional disorder, practically all stammerers should be cured. But, like others, I have seen stammerers treated competently for years by able analysts without good results. The patients, too, were intelligent and cooperative. The negative results in such cases occurred even when home and other environmental factors were carefully controlled. One must conclude from this that the fundamental question of structural disturbance also influences the development of speech. In certain stammerers one may observe a reversion of the speech mechanism to primitive childish patterns. In such a disorder sinistrality and cerebral dominance undoubtedly play a role.

It seems to me that one cannot postulate any single theory of stuttering. There are instances in which structural factors, probably hereditarily determined, are predominant. There are other instances in which the stuttering is conditioned by emotional and environmental factors, that is, by neuroses. Although I have no figures, I should say that the neuroses constitute the larger group; the smaller one, based on structural anomalies, falls into the category which Dr. Orton has discussed so ably.

Dr. Bernard C. Meyer (by invitation): In view of my brief experience of a little more than one year in the field of stuttering, I feel I should apologize for presuming to discuss Dr. Orton's paper. During this period I have had the opportunity of examining over 100 stutterers at the National Hospital for Speech Disorders. I am particularly impressed by the inadequacy of any consideration of the problem which fails to take cognizance of the frequent and pronounced fluctuations in speaking ability which occur in the history of the stutterer. I was struck by the remarkable disappearance of the stutter under such conditions. For example, many patients can take part in a play, assuming the role of another person, without displaying any stutter whatever. Others can recite speeches (which they have not written, and for which they are therefore not responsible) without any defect. Some patients fail to stutter when they are very angry. On the other hand, the stutterer is often worse when he is using the telephone. That this is related to the emotional aspects of the situation was indicated by the stutterer who said to me: "Over the telephone I cannot see the person I am talking to; I don't know whether he is smiling or not, and I can't use my own smile to win him over." Dr. Orton's reference to the tendency to stutter during the use of the dictaphone presents another instance of the same thing: One is putting down a permanent record which is ineffaceable, and one has to take the consequences, as it were. Failure to emphasize these many conditioning factors in the appearance of the stutter leads to the erroneous conclusion that stuttering is simply a disorder of speech. To me it is a disorder of speech only as long as speech is being used as a means of communication between persons who stand in an emotional relation to each other. It is for this reason, it seems to me, that stuttering is often employed by the person as a defense. I recall a patient in whom full blown schizophrenia developed shortly after treatment of his stutter was begun. I do not know that the treatment of the stutter caused the psychosis, but I do know that as the latter progressed the stutter diminished, and a recent letter from the hospital where the patient is confined informed me that his stutter was barely noticeable. The point I wish to make is that with the onset of the psychosis stuttering was no longer needed as a defense

against his anxieties. Speech is to be regarded as an executive act by means of which a person is enabled to enter into relationship with another. When such an interpersonal relationship is charged with emotional tension, speech may be inhibited. The stutter then represents a conflict—a desire to speak accompanied by a simultaneous desire not to speak, which results in various tonic and clonic spasms. The operation of inhibition of an executive act can be seen in situations other than speech. An example is psychic impotence, in which the will to perform is accompanied by inhibitory impulses representing the will not to perform, with resulting failure in erection. The same phenomenon can be seen in association with hysterical paralyses. That neural mechanisms are involved in all inhibitory phenomena there is no doubt. Just as speech is integrated through neural mechanisms, so is the inhibition of speech. However, it seems less important to know the neural pathways which are involved than to understand the psychodynamics of the inhibition.

In tests of over 100 patients for handedness, eyedness and footedness, I found that the vast majority were right handed. Less than 25 per cent had been subjected to attempts at conversion from left handedness to right handedness; so I felt that with over 75 per cent of the patients there was no reason to assume faulty cerebral dominance. In a case of right infantile hemiplegia, in which the patient was thus forced to become left handed, examination of the pyramidal tract signs on the right side showed that without a doubt the left cortex had been severely damaged from the beginning and that there could never have been any doubt of which side was dominant; yet this patient was a severe stutterer.

As for the statement that children who stutter are not frightened or inhibited, I found nearly 40 per cent of the patients to be nail biters and over 20 per cent to have enuresis, both habits being good evidence of chronic anxiety. I was also impressed with the significant number of repeated catastrophic dreams recounted by these patients, dating back to early childhood, and again indicative to me of anxiety. It is my feeling that the overwhelming number of stutterers are neurotic and that the stutter is simply that part of the neurosis which "sticks up" above the surface.

Finally, as to heredity, one cannot fail to be impressed by the large number of patients with relatives who stutter. About 61 per cent of the patients at the hospital with which I am associated have relatives who stutter, as compared with 6 per cent of the normal population. However, in making out family trees, I was unable to correlate the pedigrees with any of the usual mendelian patterns, and only in a few instances was I able to eliminate the factor of imitation with any certainty.

DR. ABRAHAM BLAU: I have been interested in stuttering and reading disability for many years, and Dr. Orton's theory has particularly intrigued me. This theory has created considerable impression on teachers, neurologists and psychiatrists, and people who are interested in the subject are divided into two groups: those who believe in Dr. Orton's theory and those who do not. The neurologists as a group tend to stand on his side, claiming that stuttering is chiefly of organic origin, while the psychiatrists take the other side and insist that the condition is purely neurotic. I should like to support Dr. Wechsler's idea that the condition of stuttering is a psychosomatic disorder and that a theory is needed that can explain both the physical and the psychiatric symptoms.

I agree with Dr. Orton that there is an intimate relation between stuttering and reading disability and the phenomenon of cerebral dominance, a relation which places these disorders in the category of organic neurologic conditions. However, when Dr. Orton stretches his theory to include the concept that stuttering is due to retraining of an originally left-handed person, the facts will not support his view. There is no doubt that there is a larger percentage of left-handed persons (or originally left-handed persons) among stutterers and persons with reading disabilities than in the population at large. However, the great proportion of stutterers do not have a history of dominance of the left cortex or of retraining from such dominance, and the great majority, perhaps 80 per cent, have definite dominance of the right cortex. It is well known that before the formulation of Dr. Orton's theory, it was common practice in schools to retrain all left-handed children to become right handed, and these thousands of children did not become stutterers. It is therefore a mistake to spread the idea that such children are in danger of becoming stutterers.

One has to explain, however, the relationship which undoubtedly exists between stuttering and cerebral dominance. There is also indisputable evidence of the neurotic basis of stuttering. It is not enough to say that the neurotic symptoms are secondary to the inferiority the subject feels when he speaks, because the history indicates that the neurotic symptoms clearly antedated the onset of the stuttering.

I think Dr. Orton unintentionally misinterpreted the psychoanalytic theory of stuttering to mean that the movements in stuttering are centered about the problem of sucking and that the stutterer is repeating the suckling movements of the infant. This idea has been mentioned,

but it is not the main point in the theory. The principal idea, in a few words, is that stuttering is a disguised expression of repressed hostility and negativism toward the environment and the people whom the stutterer has to face and talk to. In this respect I agree with Dr. Meyer's comments.

The crux of the whole problem lies in the question: What is cerebral dominance? What makes one person right handed and another left handed? The doctrine has been handed down and repeated again and again that cerebral dominance and handedness are hereditary traits. I cannot find any evidence in the literature or in patients which in any way supports this notion. On the other hand, one can find much evidence that right handedness is not inherited, but is acquired early in the person's life. The general tendency to laterality or sidedness seems to be inherited. But the trait of preferred laterality, that is, right sidedness as opposed to left sidedness, is not inherited but is acquired anew by each person early in life, and is a cultural folkway which each child is unconsciously taught by his parents and his environment. To be left sided comes to mean "to be wrong." There is thus an ethical attitude toward right handedness and left handedness. If it were a purely hereditary function, there would be no need for a moralistic attitude.

Therefore, if it is granted that handedness and cerebral dominance are not hereditary, but are acquired early in life, and that left handedness stands for wrong dominance, or an abnormality of dominance, one may get a totally different view of left handedness and of stuttering. Left handedness itself may be looked on as a symptom of negativism, of hostility to the cultural pattern. From that point of view one can understand that stuttering and left handedness may be concomitant symptoms of negativism—incidentally, but not casually, related. It can also be shown that both are based on an early infantile neurosis which affects the psychosomatic development of the neurologic status and the personality.

Dr. Samuel T. Orton: I am continually astonished at how the main point of my theory escapes almost all who discuss it—that is, the question is not whether a person is right handed or left handed but whether or not he represents an intergrade between right sidedness and left sidedness. The work of geneticists has proved that intergrades occur in every promiscuous crossing of opposite characters. It is only when pure strains are crossed that the mendelian formula is applicable, and when intergrading between right handedness and left handedness occurs, the influence of environment will be most apparent. Naturally, when a person is not strongly right handed or left handed, the much greater number of right handed persons in the environment will tend to make him right handed.

With regard to the hereditary factor, one should not depend on handedness for its demonstration, since this trait is so open to the influence of environment. In other, pure characters the hereditary character of sidedness is demonstrated. Indeed, one may even go back to the coiling of snails, in the animal kingdom, or to that of tendrils, in the vegetable kingdom. Two types of snails were discovered in two islands of the Hawaiian group which were separated by a deep arm of the sea. One of these was coiled consistently to the right, and the other, to the left. The geneticists experimented with these two pure strains of snails; three fourths of the offspring appeared to coil to the right and one fourth to the left. It is from instances of such crossing of pure stocks that the misinterpretation comes. There are no pure right-handed or pure left-handed families; hence intergrading between the two characters should be expected. Moreover, there is, as stated in my presentation, a sex factor in sidedness. Stuttering, in my records, seems likely to pass by the male line, while reading disability apparently is more commonly transmitted from mother to son. This emphasizes my point that sidedness does not follow the mendelian formula but is sex influenced and that intergrading is frequent, these intergrades representing the potential disabilities. It is just such failure to include the intergrades that has given rise to bizarre conclusions, such as those expressed in a recent article in a popular weekly magazine. That article contains misquotations and is, I believe, potentially dangerous in its recommendations.

**Use of Electroencephalography in the War Effort.** Dr. Bernard L. Pacella.

A more extensive use of the electroencephalograph in military practice is advocated. The military use of the electroencephalogram would be essentially the same as its civilian use, but greater emphasis would be placed on certain aspects of its clinical application to military neuropsychiatry because of selective factors involving the special character of the material and the peculiar exigencies of military practice. Small portable electroencephalographic units which do not necessitate elaborately prepared rooms for the taking of records are now available.

One of the more important problems confronting neuropsychiatrists concerns the proper "screening" of persons who are to be inducted into the armed services; it is believed that the

electroencephalogram can be of appreciable value as an aid in this process. In this connection, it is recommended that routine simplification of electroencephalographic examinations, or at least a much wider use of such examinations, be employed in conjunction with the medical examination of all incoming military personnel. It is generally observed that epileptic recruits often deny having the disease at the time of induction into the Army and that many epileptic persons could be readily eliminated by routine electroencephalographic observations. It should be added, however, that an abnormal or a convulsive electroencephalographic pattern does not necessarily mean that the recruit is subject to convulsions. Nevertheless, the men exhibiting abnormal records could be subjected to careful scrutiny of the personality and a careful history could be taken, inasmuch as an extensive literature points to a correlation between psychopathologic processes and abnormal electroencephalograms even in the absence of evidence of any cerebral lesions.

For the purpose of carrying out large scale electroencephalographic examinations, a simple, rapid system of electrode placement which would entail the running off of only relatively short records, i. e., of about five minutes' duration, is suggested. The apparatus employed utilizes six electrodes placed on a flexible plastic frame. This can easily be adjusted and firmly fixed onto the head so that the electrodes are over the corresponding prefrontal, precentral and occipital regions of the brain on each side. With this system it is possible for one technician to obtain at least six records in an hour.

The use of the electroencephalogram in military neurologic and psychiatric hospital practice would be essentially the same as that in civilian neuropsychiatric practice. Electroencephalograms can be extremely useful in cases of trauma to the head and in some instances of cerebral injury one may use the electroencephalographic records as the main criteria, in the absence of clinical symptoms, to determine when a patient is to be returned to active duty.

A word should be said regarding the utilization of the electroencephalogram in certain research activities in the armed services. Valuable studies can be conducted to determine further correlations between injuries to the head and electroencephalographic changes. Some light can be shed on the question whether persons in whom post-traumatic epilepsy developed after an injury to the head had manifested electroencephalographic abnormalities prior to the traumatic incident. Many other research problems could be conducted on a large, well integrated scale.

DISCUSSION

DR. S. EUGENE BARRERA: Dr. Pacella has raised many interesting questions about the use of electroencephalography in both hospital practice and in the screening tests employed in the selection of men for military service. Undoubtedly it could have application in both. As Dr. Pacella has emphasized, its use in military hospitals will essentially be similar to its use in the average neurologic or general medical hospital. It will have two main uses: first, as a diagnostic aid, and in that sense it will be employed to localize lesions or to diagnose rather obscure conditions, and, second, for purposes of record in discharge procedures from military service, a use which I think would be important. I am told that at times it is difficult to make a definite diagnosis of epilepsy or convulsive seizure in a case in which the soldier is hospitalized for a disorder which is suspected to be epilepsy. I am told the attack has to be witnessed by some one before it can actually be diagnosed as epilepsy and the discharge from the service made. The suspicion and the clinical impression, together with a positive electroencephalographic record (for I believe it is generally conceded that an experienced electroencephalographer will in a large number of cases detect a pattern which is abnormal and thus provide additional evidence), should be sufficient to warrant the recommendation for discharge because of a convulsive disorder.

Again, electroencephalography should be employed in the elimination or detection of certain hysterical manifestations; here its use would be of importance, not only as a guide to treatment, but in avoidance of confusion with convulsive disorders. Dr. Pacella has pointed out its possible use after cerebral trauma in differentiation of conditions which have an organic basis and those which probably are not associated with cerebral trauma.

The question of the inclusion of the electroencephalogram in the routine examination of men for the armed services is of interest. A large number of men whom one might call potentially epileptic will show definite pathologic records which a good electroencephalographer can pick up, and if this can be done rapidly and by a method such as Dr. Pacella has utilized, the examination will be extremely important in elimination of a group of potentially epileptic recruits. Whether an abnormal electroencephalogram should be included in the military record, and placed against a man, and whether, if it is considered positive for epilepsy, with no other evidence in the history, it should be sufficient to eliminate a man from military service, I do not know. The brevity of the examination raises a serious question. The test might be better applied in the selection of officers, in which the examination can be, and is,

prolonged and in which, if something abnormal is found, such as slightly elevated blood pressure, the observation is put on the record and the man is submitted to repeated examinations. Perhaps he may, if no other evidence of epilepsy is found, get in by signing a waiver. When the electroencephalogram is definitely pathologic and the rest of the evidence is negative, and when the candidate can be subjected to repeated examinations for four or five days, the question arises whether, on the basis of the abnormal electroencephalogram, the man should be excluded or whether a waiver should be signed which would take into consideration the recognition of the possible epileptic status. I do not know just what the procedure would be in that contingency, but I feel that potential epilepsy can be detected by the electroencephalogram and that it might rather be important to have the evidence on record, if not to debar the candidate completely, at least to have it there for future reference.

DR. RICHARD BRICKNER: This could be done before induction, without its ever being made part of the army record.

MAJOR BENJAMIN H. BALSER: I feel it is of extreme importance to emphasize Dr. Pacella's statement that epilepsy constitutes one of the major and annoying neuropsychiatric problems in the armed forces. Regulations require that the patient be seen in an attack by a medical officer or that there be positive neurologic evidence, such as that offered by the electroencephalogram or the pneumoencephalogram. It is important to realize that most of the patients with idiopathic epilepsy who are seen in the army do not represent the deteriorated type encountered in state institutions. The mental status of these men is usually intact. The effect of epileptic personnel on the morale of other members of the unit must be considered. It does not do the other soldiers any good to see one of their bunk mates have a convulsion. Electroencephalography is not available to most of the army hospital units, certainly not to field units overseas; therefore, Dr. Pacella's suggestion with regard to the use of this method as a practical preinduction measure is certainly welcomed by the examining officers of the induction boards. It is obvious that such a procedure would eliminate the majority of epileptic persons from the services, and that thus more time would be available for other vital work.

Preinduction records would be of extreme value in cases of injury to the head. With mechanization of the armed forces to the degree that exists at present, such injuries constitute the largest single problem encountered in the neuropsychiatric service at Mitchell Field. There are more patients with such injuries than there are men with psychoneuroses. Cases of traumatic epilepsy are fairly frequent, and it is in such cases that the preinduction record is of particular value.

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## PHILADELPHIA NEUROLOGICAL SOCIETY AND PHILADELPHIA PSYCHIATRIC SOCIETY

HAROLD D. PALMER, M.D., *President of the Philadelphia Psychiatric Society, in the Chair*

*Joint Meeting, March 12, 1943*

**Intramedullary Gliomas of the Spinal Cord.** DR. HENRY A. SHENKIN and DR. BERNARD J. ALPERS.

This study consists of the analysis of 27 verified cases of glioma of the spinal cord, with a thorough review of the literature. The incidence, growth characteristics, relation to syringomyelia and general pathologic features are discussed. In 18 cases of this series histologic verification was made, the tumor being ependymoma in 7 cases, astrocytoma in 10 cases and ganglioneuroma in 1 case.

The age distribution of these tumors was the same from the second to the sixth decade of life. The duration of the clinical course of intramedullary glioma of the cord did not differ significantly from that of the extramedullary type. Gliomas of the cauda equina had, however, a distinctly prolonged course. The first symptom in 16 of the 27 cases was pain, which was of rootlike nature in 6 cases. Muscular weakness was the mode of onset in 7 cases, and in 5 cases the illness was initiated by numbness or paresthesia. Remissions were noted in 3 cases.

Analysis of the symptoms revealed that pain was practically a constant feature. Typical root pain was not unusual in cases of intramedullary tumor, and it occurred at any time during the course of the illness. Associated with the pain were paresthesias. Once these symptoms appeared, they were apt to be persistent and progressive. Motor symptoms either ushered in the clinical picture or developed within a short time after onset. The type of motor disturbance varied with the level of the lesion; an amyotrophic syndrome was likely to develop with tumors of the cervical portion of the cord. The most significant sign serving

to distinguish intramedullary and extramedullary tumor was the alteration in sensation. This consisted of relative sparing of the more distal segments and more pronounced involvement of the proximal segments. A Brown-Séquard syndrome was encountered at times, and anogenital disturbances were absent.

Sphincter disturbances, as a rule, were likely to occur late in cases of intramedullary tumor, and they by no means appeared in every instance (60 per cent). The differential diagnosis of intramedullary and extramedullary tumor was summarized and discussed.

DISCUSSION

DR. FRANCIS C. GRANT: It is a good thing to have one's ideas on certain subjects reoriented. For the past ten years I have been teaching students that one way in which an intramedullary and an extramedullary tumor could be distinguished was the presence of pain as a preliminary symptom with extramedullary tumor and the disturbance of sphincter control as an early symptom with an intramedullary lesion. From Dr. Alpers' analysis of this rather limited group, neither of these diagnostic criteria seems to hold as well as I had assumed. I did not realize that in so many cases of intramedullary tumor of the cord symptoms began with segmental pain or that loss of sphincter control appeared so late in the course in a high percentage of cases.

I was pleased to hear that intramedullary tumors comprise only roughly 20 per cent of all lesions of the spinal cord. The percentage of benign tumors involving the spinal cord seems to be definitely higher than that of benign tumors of the brain.

Dr. Alpers' statements with reference to pain were interesting. Root pain is familiar; "spinal pain" and tract pain are unfamiliar. The physiology of pain is still mysterious. Grasp a posterior root and the patient promptly experiences severe localized, segmental pain. Yet the adjacent spinothalamic tracts may be incised, as in chordotomy, without any pain. How does the physiology of pain conduction change with respect to its interpretation by the patient's sensorium, between the posterior root and the spinothalamic tract? This, of course, is not a fair question, as Dr. Alpers was not discussing primarily the subject of pain, but if he can throw any light on this question it would be much appreciated.

DR. ALEXANDER SILVERSTEIN: Is myelography of any help in differentiation of intramedullary and extramedullary tumor?

DR. GABRIEL SCHWARZ: Was there any change in the sensory or the motor picture after lumbar puncture in Dr. Alpers' cases? Often examination thirty minutes or an hour after lumbar puncture, whether there has been a partial or a complete block of the spinal subarachnoid space, reveals a change in the sensory level or an increase in motor signs. This is true with extramedullary lesions of the spinal cord and has been explained by the release of the supportive cushion of spinal fluid below the mass, so that greater pressure is exerted on the spinal cord and its vascular bed. I wonder whether such changes were noted in this series of intramedullary tumors of the spinal cord.

DR. BERNARD ALPERS: With regard to Dr. Grant's question concerning the types of pain, I should have preferred not to mention "spinal pain" except as a term handed down in the literature.

Pain in the lower part of the back appears to be a feature of intramedullary glioma. Tract pain is due to irritation of a spinal tract and is totally different from ordinary pain; it is usually described as diffuse, burning or boring and has no root and no peripheral distribution.

Myelographic studies showed 7 cases of complete block and 9 cases of incomplete block, the latter being demonstrated by the displacement of the column of iodized poppyseed oil by the tumor.

I do not have any data on the changes in the picture after lumbar puncture; so I cannot answer Dr. Schwarz's question.

**Group Psychotherapy.** DR. SAMUEL B. HADDEN.

Group psychotherapy is not a new method of treating maladjustments; it has been used for centuries and has been effective in the management of various diseases. In the neurologic department, with selected patients, it saves time and gives better results than brief individual interviews.

Sessions are distinctly informal. After a few preliminary remarks, the effects of various emotions on body functions and of physical tension on the nervous system are described, this discussion being followed by instruction in methods of relaxation. When the group has relaxed, encouraging suggestions are repeated, and the dynamics of some particularly common symptom is explained. Hypothetic cases are discussed for their psychologic benefit.

Conflict and symptom production, the duality of the personality, repression and harmonious compromise, the desirability of dominance of intellectually directed behavior versus that of purely emotional reactivity are all explained and stressed. A written account of the symptoms and personal history is required, the mechanism of catharsis being important. While the process of transference and some element of rivalry are beneficial, emotional reeducation and encouragement from the group director and the fellow members seem to be more important.

The results obtained by the group are most encouraging, and it is felt that the class technic will see wider application and will be of special benefit in rehabilitation of psychoneurotic personnel of the armed forces.

DISCUSSION

DR. ROBERT A. MATTHEWS: Dr. Hadden has long been interested in this type of work; he believes in it, and he has a personality which allows him to impress a group of patients gathered together for this purpose. His method of repeating certain basic psychotherapeutic concepts each evening because a new, or several new, patients are present allows repetition to play its educational role. Then the fact that the patient is asked to give a review in written form of what has happened to him during the previous week, which the leader can go over in some detail, pointing out each patient individually in a kindly, interested way, provides for each a personal identity. The patient feels that he has a place of his own in the group, a factor which seems to be of real significance in making this therapy useful. Then the whole spirit and atmosphere of the group, largely a permeation from the personality and technic of the leader, enhance the benefit that each patient gets from the treatment.

In a large city like Philadelphia many people, especially the shy and sensitive, need socializing opportunities. Many of the patients are hungry for affection. They need to be able to go to a person, speak to him and call him by his first name, which I am sure must happen among the members of these groups after a time. Although there is a group atmosphere, there is no group politics. The leader has a monopoly on the control of the group. There are no cliques to eliminate a new patient, since the group is changing constantly.

Constant reassurance and suggestion and reeducational factors play a part, of course; these are an integral part of any type of psychotherapy.

I see one important weakness in the setup—that is, many of the patients probably have problems involving the deeper layers of their personalities which cannot be handled completely by group psychotherapy. If the setup is enlarged, as it will be in the future, patients should have the opportunity to see a psychiatrist at intervals for private interviews.

The final period of relaxation, with instructions on how to relax, impressed me as containing an element of mass hypnosis, which is not a bad thing. In group psychotherapy there may be a kind of camp meeting spirit, with public confession, which probably has a purging effect.

This form of treatment carries a message to a sizable number of people who need it, since the psychiatric personnel needed to give individual psychotherapy is not available. Certainly, the most intimate and elaborate form of psychotherapy, psychoanalysis, is by necessity confined to an infinitesimal number of people in the community, so that the knowledge and experience of the elaborately trained physician is limited to a few persons, and the number of patients who can be adequately treated by the ordinary psychiatrist is not great. After this war a tremendous number of people will require help, with few psychiatrists available to provide it.

DR. O. SPURGEON ENGLISH: I have often thought that many general practitoners and specialists in fields other than psychiatry do not give psychotherapy because they are intellectually too lazy to formulate a few simple explanations with respect to emotion and symptom formation in which they actually believe. Consequently, when a neurotic patient comes to them, they have not prepared themselves for a psychotherapeutic explanation of his neurosis, which they could easily do in half an hour, and so they write out a prescription for a pill. I do not think any formal presentation Dr. Hadden could make here would do justice to the manner in which he conducts his class.

I shall begin by stating what, to my mind, are the limitations of group psychotherapy. People are reluctant to talk about matters that are close to them—particularly about their love lives, their hostilities and their weaknesses. There is no doubt that, in the present state of culture, people feel it is natural to conceal things about themselves. Perhaps five hundred years hence there will be such awareness of human weakness in general that people will be at home with these things and there will not be so many matters about which they are sensitive. They cannot quite talk of such subjects to a group or to a leader when others are present. Any one here needs only to recall how often in a medical meeting he has had something to say but he did not have the courage to say what was on his mind and shortly

the opportunity was gone. I am sure many patients in the group want to ask questions, but it is difficult for them to get used to the presence of others. If physicians are sometimes reluctant to speak their thoughts on a medical subject, patients are even more so about their personal problems.

The matter of expediency is obvious; so I shall simply say this: In a group there is not quite that close relationship between the leader and the patient which is present in private interviews, and one cannot make the close personal appeal to each one; nevertheless, twenty-five people in a class can draw inspiration and confidence from one another and can learn from a leader rather easily. I should say that there is roughly 90 per cent as much transference of confidence and interest in the group session as in the single interview. The 10 per cent of rapport which is lacking may be extremely important in some cases but, fortunately, not in all. Father Devine inspires thousands of people and Hitler influences millions, and in the psychotherapy group the leader will draw twenty-five people toward him nearly as far as he can draw one patient. That is important when one is imparting information and suggestions and is asking patients to do away with their fears and behave more naturally.

The objection, then, that I raise to group psychotherapy is the reluctance of patients to bring their deeper feelings into the discussion. Nevertheless, I believe they can learn a great deal about love, hate and aggression which they can use outside the sessions. They may not be able to state their personal problems verbally; nevertheless, they make acquaintance with psychologic truths which may be useful in the home or at work.

Group psychotherapy has many things of value, and expediency because of the war is not the only reason for its growing popularity. It is good, likewise, to challenge the initiative and resourcefulness of psychiatrists. The use of this method will increase after the war. As people come to have more knowledge about symptoms and emotions, it will, of course, be easier to carry out psychotherapy, for the patient will know more and will come to treatment in a more receptive frame of mind. In group psychotherapy an hour (the time, I believe, which Dr. Hadden gives to a session) allows the patients time to absorb what is said; this is necessary in utilization of the therapy. One cannot give a patient ten minutes of psychotherapy and expect results. Often twenty minutes is inadequate. But if the patient has an hour in which he can get away from his everyday life and come into a psychotherapeutic atmosphere, he can absorb much, even in a group.

Dr. Howard P. Rome: I agree with Dr. Hadden on the beneficial results of group psychotherapy. In my work in a naval hospital I have had the opportunity of treating somewhat over 800 patients in seven months by this method.

The situation in military life is somewhat different from that which Dr. Hadden has encountered, and hence lends itself even more completely to this procedure. Collective action is the essence of all military situations. This attitude is carried over into the psychotherapeutic regimen as the rationale for group psychotherapy. By the patients pooling their insecurity, affiliations develop.

Participation in the plan is on a twenty-four hour a day basis. It is equally important that sleep be assured by the use of adequate sedation. With sleep, recreation and reeducation all planned, the patient is relieved of the burden of undirected lulls.

Although the greater effectiveness of the treatment has been seen with the psychoneuroses, the method is not without benefit for the psychoses. The symptoms of patients with psychoses are more easily controlled, while with a high percentage of psychoneurotic patients remission of the entire syndrome has been accomplished.

Dr. Samuel B. Hadden: I want to thank the discussants for their comments on this presentation, as well as on one of the sessions which they attended. Both commented on the socializing aspects of group therapy; it seems to me that this factor gives added effect to the psychotherapeutic procedures which one utilizes in private sessions. In addition to his being provided with sound psychotherapeutic principles, the patient in the group is given a forum and is made to feel part of an organization, and so loses much of his feeling of loneliness.

Dr. Matthews has suggested that the portion of the session "devoted to relaxation" is a bit like hypnosis. Assuredly, this is an attempt at light hypnosis in order to increase the receptivity of the patient to suggestion and to psychotherapeutic direction. Although the element of public confession may appear to be present in the group session, I have not had any revelations of intimate details before the group, but the particular problems causing the conflict of certain patients in the group may be presented by the leader without his indicating the person whose problem is presented. In this way the patient not only hears the opinions of those about him but is encouraged to participate and to present his views on the solution of his own problem, a method which forces him many times to regard his situation objectively.

A typical problem discussed is that of the patient who asked: "Will you please discuss my problem? I should like to have suggestions as to what I should do about my father-in-law and mother-in-law, who have moved in on us." This patient, incidentally, received the solution of his problem by his being directed to Old Age Pension.

There have been evidences in the group of some antagonism toward the therapeutist. One woman who attended the meetings of the group in its earlier days resented the fact that she had been referred, but she continued to come, though she never reported any improvement and at times her attitude toward the director was belligerent. On one occasion a newly referred patient asked a question: "Do you mean to suggest that I will be relieved of my symptoms by listening to lectures and talking about it? I can't see the sense of it." Before I had the opportunity of replying, the patient who had manifested antagonism for six months raised her hand and asked if she might answer "that woman." For the first time she then described "the unbelievable benefits" which she had experienced by attendance at the group discussions. She gave encouragement to the doubter to continue in attendance, and from that day on she was a very active participant in the discussions, until she discontinued attendance when she obtained employment.

Dr. Matthews has expressed surprise that patients discuss their difficulties so freely before the group. That is because they are deadly in earnest. As a result of my interest in group psychotherapy, I was invited to attend a meeting of the group known as Alcoholics Anonymous; there I saw the same sincerity, which enabled persons to discuss their own difficulties and present their opinions in an impressive and forceful manner. We as physicians are sincere in our work; these patients are just as sincere in their desire to obtain assistance, and when given the opportunity, they will present their views and discuss their difficulties.

**The Morgagni-Stewart-Morel Syndrome: Report of a Case, with a Pneumoencephalogram.** DR. MATTHEW T. MOORE.

The triad of hyperostosis frontalis interna, obesity and virilism, originally described by Morgagni in 1765 and later expanded by Stewart and Morel to include neuropsychiatric and endocrine features, was discussed from the etiologic, pathologic and symptomatic points of view. A woman aged 39 had a history of headaches, drowsiness, convulsive seizures and psychoneurotic manifestations for ten years. Roentgenographic studies revealed the "metabolic craniopathy" of Moore, and the pneumoencephalogram showed pronounced cortical atrophy of the frontal and parietal lobes, atrophy of the island of Reil and moderately advanced internal hydrocephalus, with asymmetry and irregularity of the lateral ventricles.

DISCUSSION

DR. GEORGE D. GAMMON: One of the difficulties I have with respect to this disease is in getting the symptoms into focus. Last year Dr. J. F. Galbally made a survey of the cases at the Hospital of the University of Pennsylvania, a general hospital. The number of cases in the files of the department of roentgenography in which this diagnosis had been made was 180 or 200.

Of this number, epileptic attacks occurred in about 4 cases, and electroencephalographic studies revealed no abnormality of the brain waves. The convulsive seizures were slightly atypical of the ordinary epileptic attack.

The point I wish to make is that in some series epileptic seizures have been encountered in 30 per cent of cases, whereas in our series, and in others, the incidence was 2 per cent. Other abnormalities and mental changes ascribed to this condition have varied in frequency in different series; so I have wondered whether the symptoms associated with this deformity were not due to the type of material under consideration, and perhaps were purely coincidental. For example, the incidence of mental symptoms should be high among patients with hyperostosis in a hospital for mental diseases and low among such patients in a general hospital. May I ask Dr. Moore's opinion with respect to the symptoms of this disorder?

DR. MATTHEW T. MOORE: The discussion by Dr. Gammon presents one of the difficult diagnostic problems in evaluation of this syndrome. It must be borne in mind that the internal hyperostosis may appear rather early in life but may not be discovered until adult life, when the lesion may be present as part of or as the complete clinical syndrome. Indeed, it is maintained by some authors that the cranial changes are not necessary, but that merely the endocrine and mental aspects are essential, to make the syndrome an entity. This assertion may be open to question.

With regard to the relation of cerebral atrophy to pressure by the expanding bone, it has been shown by Stewart that the one is not the result of the other. He reported the case of a woman aged 65, who presented cerebral atrophy, the result of a thrombotic lesion, in which the degree of the internal hyperostosis was greater on the side opposite the cerebral atrophy.

Some patients do not present mental symptoms during the early phase of the metabolic craniopathy. Others show relatively mild psychoneurotic symptoms, and their condition is diagnosed as a psychoneurosis or as hysteria. Beadles, in 1898, reported on a large number of cases of hyperostosis interna occurring among the patients in institutions for mental disease. Many of these patients remained in the hospital for many years, and their condition ultimately developed into frank dementia.

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## BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

WILLIAM G. LENNOX, M.D., *Presiding*

*Regular Meeting, March 25, 1943*

PRESENTATION OF CASES

**Myoclonus Epilepsy.** DR. WILLIAM G. LENNOX.

**Repair of Cranial Defects.** DR. WALTER WEGNER.

**Visual Agnosia.** DR. ALEXANDRA ADLER.

**Leber's Hereditary Optic Nerve Atrophy.** DR. H. HOUSTON MERRITT.

**Section of Anterior Spinal Roots for Prevention of "Mass Reflex" After Spinal Transection.** DR. DONALD MUNRO.

**Spinal Bifida Occulta with Myelodysplasia.** DR. RAYMOND D. ADAMS.

**Acute Onset of Hemiplegia with Convulsions in Childhood.** DR. D. DENNY-BROWN.

# Book Reviews

**After-Effects of Brain Injuries in War, Their Evaluation and Treatment.** By Kurt Goldstein, M.D. Foreword by D. Denny Brown, M.D. Price, $4. Pp. 244, with 49 illustrations. New York: Grune & Stratton, Inc., 1942.

It is a common observation in clinical neurology that patients with lesions involving the cerebral cortex exhibit a notable variability and inconsistency in their responses to test situations. In this volume, Dr. Goldstein, through his portrayal of the psychopathology of the patient with an injury to the brain, throws much light on the mechanisms of this phenomenon. The author contends that the person who has sustained an injury to the brain in order to readjust himself to the world has withdrawn from numerous points of contact with it and has thus attained a readaptation to a shrunken environment. Within his limited sphere, the patient can function relatively smoothly, but in a situation with which he is no longer equipped to deal, his whole behavior becomes disturbed. "He looks dazed, changes color, becomes agitated, anxious, starts to fumble, his pulse becomes irregular; a moment before amiable, he is now sullen, evasive, exhibits temper, or even becomes aggressive." The author terms this a response to a catastrophic situation. These symptoms are not the direct result of damage to the brain; they are "the expression of the struggle of the changed organism to cope with the defect."

Another group of symptoms reflects the tendency of the patient to build up substitute performances which allow him to escape this struggle. He may, for example, camouflage an inability to calculate by memorizing the correct answers to arithmetical problems. One must be cautious in evaluating results, therefore, as in a test situation a patient may give a correct response but one attained in an incorrect, i. e., abnormal, manner. Furthermore, on a subsequent occasion in the same, or in a closely similar, performance, there may be complete failure if the situation does not permit the patient to take his roundabout way of approach. It is important to remember that factual failure in a task does not necessarily mean that the ability to perform it is completely lost. "The patient's failure to act, to do anything at all, may spring from his feeling of apprehension, of uneasiness about the result he might reach: he is afraid that a wrong result will get him into a catastrophic situation." If the patent is in good rapport with his physician, he may be somewhat reassured against the dreaded catastrophic situation and may be readier to risk wrong answers. "Hence the fact that different records may be obtained by different physicians from the same patient."

A third group of symptoms results from the impairment in the abstract attitude of the person with an injury to the brain, i. e., inability to shift voluntarily from one aspect of a situation to another, to keep in mind simultaneously various aspects of a situation, to grasp the essential of a given whole, to abstract common properties and to think or perform symbolically. Patients often may be able to fulfil tasks which can be performed in a concrete way but fail when an abstract attitude is necessary.

With these considerations in mind, the author stresses the fact that if psychologic laboratory tests are to give a true picture of the patient's abilities, there must be careful observation of his behavior over a long period, with keen insight into and understanding of his psychopathologic difficulties. Only in this way can one evaluate his mental functions, his general level of performance and his potentialities with regard to various kinds of work after discharge from the hospital.

The case material for this study was made up of patients with injuries to the skull and brain caused by gunshot wounds and observed during and after World War I. About 2,000 patients were examined systematically. Of this group, about 100 patients remained under the observation of the author for about ten years, being seen daily during the first years and once a week or once a month later. A larger group was seen at least once or twice a year for approximately ten years.

Of the psychologic tests employed, the tachistoscopic examination proved of great value. In this procedure, figures or other objects are exposed for a short time (one-fifth or one-tenth second) on an opaque glass screen, and the patient is required to tell what he has seen or to make a drawing of it on a piece of paper. "In this way disturbances can be disclosed which escape recognition when investigated in the usual manner. . . . Slowing down of mental processes, disturbances of attention, of memory, of the visual capacity in different directions, disturbances of reading (alexia), of visual recognition of objects (agnosia), as well as defects of the visual field, disturbances of color vision, aphasic symptoms [may be

brought out]." Reaction tests, involving either a simple reaction to a suddenly appearing stimulus or a choice of reactions, were useful in determination of the patient's endurance, capacity to reason and fatigability. These same characteristics were also tested by the Kraepelin method of continuous addition, the technic of the original test being somewhat modified by the author. Motor capacity was studied by means of the finger ergograph, the large ergograph and the dynamometer.

Small workshops were made a part of the hospital in which this material was studied. Suitable patients were given set tasks for a number of hours each day in these shops, careful records being kept of all details of their performance. The results obtained in the workshop showed a high degree of conformity with the results of the performance tests mentioned.

After the patient's psychologic and neurologic status had been accurately determined, treatment was instituted. The section on treatment is concerned almost exclusively with the aphasias. It contains a number of illustrative case histories, showing how therapy has to be geared to the requirements of the individual case. Previous surveys of some patients had indicated that the brain was not so severely damaged as to preclude restitution of function. Retraining was, therefore, aimed at helping the patient regain his lost performance capacity. In other patients damage proved to be so great that therapy had to be directed toward building up other, compensatory performances in the same field, or, in some patients with extremely severe injuries, compensatory performances of a totally different kind. As some patients showed steady improvement over long periods, long term treatment is recommended.

In discussing the problem of rehabilitation, the author states: "We made every attempt to prepare each man to continue his former vocation. However, it became more and more evident that it was often better for both worker and employer to train the patient for a new type of work that he could perform with relatively little skill, than to permit him to continue in his old vocation, where at best he could do only mediocre work. In relation to the choice of vocation, it is necessary to consider the special impairment, the original skill, and also the character of the man."

This book contains a vast number of keen clinical impressions based on the author's own large experience. The material is not presented, however, in a systematic, statistical manner, and the number or the percentage of patients in whom a particular finding has been noted is never stated. It is regrettable that the text is rather poorly footnoted, so that it becomes difficult to use the extensive bibliography of 197 items in conjunction with it. Although the author emphasizes the need for differentiation of organic, psychoneurotic and malingering factors in cases of head injury, he gives no hint as to a systematic procedure in this regard. The positive values of the book far outweigh its shortcomings, however, and it is to be highly recommended to all interested in this field.

**Human Neuroanatomy.** By Oliver S. Strong, formerly Professor of Neurology and Neurohistology, Columbia University College of Physicians and Surgeons, and Adolph Elwyn, Associate Professor of Neuroanatomy, Columbia University College of Physicians and Surgeons. Price $6. Pp. 417, with 320 illustrations. Baltimore: Williams and Wilkins Company, 1943.

This is one of a number of good textbooks of neuroanatomy that have appeared since 1942.

There are two types of readers to be satisfied by such a book as this; the first and more important, and certainly the least consulted, is the undergraduate student of medicine. This book would appear to answer the student's need. The material is organized and written so that he may find collateral reading no more difficult than the intricacies of the subject dictate. Illustrations are liberally interspersed in the text; they are large and clear, particularly those made from myelin sheath stains. The student should be stimulated by the reasoned consideration of function at the end of the chapters in which it is indicated.

Also to be considered in the execution of a text of this sort is the practitioner of medicine, and particularly of neurology. He usually is especially interested in blood supply, not only arterial nutriment but venous drainage. Illustrations pertaining to the vascular system are not as liberal here as in some of the other current textbooks of neuroanatomy, although the description in the text on this point is certainly adequate. Lamination of tracts in the brain stem, a peculiarly evasive, though recurring topic for the clinician, is not clarified for him here, since it is not to be found in the index, nor did the reviewer find indications of it in a particular search of the text and the illustrations.

This is surely one of the books that must be considered in selection of a text for students, and it is probably one of the several compendiums that the worker intimately concerned with the neurologic field would want among his reference books.

**The Role of Nutritional Deficiency in Nervous and Mental Disease.** Research Publications, Association for Research in Nervous and Mental Disease. Volume XXII. Pp. 215. Price, $4. Baltimore: Williams & Wilkins Company, 1943.

This book consists of a series of articles contributed by various authors and represents the proceedings of the Association for Research in Nervous and Mental Disease at its meeting in New York in December 1941.

The material is divided into two parts. Part I deals with "contributions from the fundamental sciences" to the subject of nutritional deficiency as it affects the central and peripheral nervous systems. This contains the data obtained from biochemical, physiologic and animal experimentation. Part II deals with the "clinical aspects" of disease of the nervous system resulting from nutritional defect.

The larger part of the volume is devoted to biochemical studies of the vitamin B complex and its components and to the effects of deficiency in these factors as manifested in disease of the nervous system. Other chapters deal with vitamins A and E and with phenylpyruvic oligophrenia and pernicious anemia. There are several good general discussions of nutritional deficiency.

Some repetition in presentation of the material is inevitable. There is much of value in this volume. It sets forth clearly most of what is known about nutritional deficiency as it is reflected in the nervous system. The most commendable feature of the book is its stimulating quality. The field of deficiency disease of the nervous system is an extensive one, and much remains to be done; the book contains many leads for further investigation and much promise of what is to come. It is recommended for reading by the internist and the neuropsychiatrist.

**Vision: A Study of Its Basis.** By S. Howard Bartley. Price, $3.50. Pp. 350, with 78 illustrations. New York: D. Van Nostrand Company, Inc., 1941.

This modestly sized, but excellent volume combines the features of a general handbook with those of a specialized monograph. It offers at once a general survey of the basic subject matter and a specialized treatment of certain topics in the neurophysiology of vision in which the author has been particularly interested. Prof. E. C. Boring, who writes a brief preface, points out that historically important books in the field of vision have usually been of this sort, and the reader does get the feeling that Dr. Bartley has done considerably more than merely summarize current available knowledge in the field.

The book, while less than 350 octavo pages, contains a veritable mine of information, and it is this fact which gives it the character of a handbook. Most of the topics are of necessity treated briefly, but the descriptions of the phenomena discussed are always clear, to the point and accompanied by up-to-date references at the end of each chapter. Among the more fully treated topics are the phenomena of flicker, the problems of neurologic adaptation and cortical response and the electroretinogram. As might be expected, relatively little space is devoted to the purely psychologic aspects of vision. On the other hand, much material in the field of electrophysiology is included which, as the author points out, has not hitherto appeared between the covers of a book.

All in all, it is a book which will be of value not only to the student and the specialist but to any one who is interested in the basic facts, as well as the most recent advances, in the field of vision.

**Outline of Psychiatry Case-Study.** By P. W. Preu. Second Edition. Price, $2.75. Pp. 272, plus index. New York: Paul B. Hoeber, Inc., 1943.

As the preface states, "The manual is not intended to be used as a textbook of psychiatric diagnosis and treatment but as an aid in eliciting the facts on which diagnosis and treatment are based." This aim is admirably fulfilled. The book begins with a general review of the technic of psychiatric interviews, including such practical hints as "The traditional white coat is decidedly not an asset in psychiatric office practice." It goes on to give a rather comprehensive, systematic list of the topics to be discussed, and even the specific questions which might be asked, during such an interview. Methods of observation of behavior are presented, including an outline of the procedure to be used with comatose patients. Psychologic tests are reviewed, and the important points in the physical examination of psychiatric patients are listed. A separate section of about 100 pages is devoted to an outline of the special methods of history taking and examination suitable for children.

This book is to be highly commended for the use of students, nurses, practitioners and physicians in training in psychiatry.